WEBVTT

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00:00:34.440 --> 00:00:45.840
Amy Friedlander: Good afternoon. Ordinarily money's parish, or would have the pleasure of welcoming our distinguished guest, but unfortunately he cannot be with us and he sends his regrets.

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00:00:46.290 --> 00:00:52.860
Amy Friedlander: On his behalf as well as on behalf of NSF and the Directorate for Computer and Information Science and Engineering

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00:00:53.190 --> 00:01:09.480
Amy Friedlander: The Directorate for mathematical and physical sciences and the Directorate for biological sciences, I am delighted to welcome and to and to introduce Dr Romy morrow. I'd also like to welcome our colleagues from MTS

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00:01:12.240 --> 00:01:15.240
Amy Friedlander: Dr. Dr. Andrew love injure

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00:01:16.860 --> 00:01:34.740
Amy Friedlander: Who will be helping me moderate the questions as our customer at these events. Dr. Morrow will join NSF staff at 4pm Eastern for more freeform conversation. Please type your questions into the Q AMP a box and Andrew and I will ask Dr. Omar to respond to them after her talk

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00:01:36.690 --> 00:01:43.500
Amy Friedlander: Dr. Morrow is a professor and dad Chair of chemistry and biochemistry at the University of California, San Diego.

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00:01:43.950 --> 00:01:49.980
Amy Friedlander: Her research focuses on development of computational methods in biophysics for pharmaceutical applications.

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00:01:50.460 --> 00:02:04.350
Amy Friedlander: She obtained her bachelor's degree in Chemical Engineering from the University of Illinois at Urbana Champaign and spent two years as a staff scientist at Kraft Foods before returning to you I UC to pursue her PhD in chemistry.

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00:02:05.010 --> 00:02:17.850
Amy Friedlander: After a postdoctoral fellowship at University of California, San Diego. She joined the faculty at University of California, Irvine with appointments in the departments of Pharmaceutical Sciences computer science and chemistry.

10
00:02:18.360 --> 00:02:34.950
Amy Friedlander: In 2010 Dr Amaro received both an NIH directors new innovator Award and the Presidential Early Career Award for scientists and engineers, she returned to UCSD in 2011 in the department of chemistry and

biochemistry.

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00:02:35.430 --> 00:02:43.980
Amy Friedlander: And directed the national biomedical computational resource from 2013 to 2020

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00:02:47.010 --> 00:02:49.050
Amy Friedlander: Hi, I'm having some problems today.

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00:02:58.140 --> 00:02:58.920
Amy Friedlander: Apologies.

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00:03:05.850 --> 00:03:16.590
Amy Friedlander: Darfur mom means active and public outreach and science communication, a high school student she commented one the 2013 Siemens competition in math, science and technology.

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00:03:16.920 --> 00:03:22.110
Amy Friedlander: The 2013 Google Science Fair and the 2014 Intel science talent search

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00:03:22.800 --> 00:03:31.590
Amy Friedlander: Last February, Dr. Morrow and her team were able to produce the first atomic level simulation of the full length SARS Cody to spike protein.

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00:03:31.980 --> 00:03:40.680
Amy Friedlander: Which was published in the ACS journal central science, science and subsequently described in a number of press releases and released on Twitter in March.

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00:03:41.220 --> 00:03:50.160
Amy Friedlander: A second paper co authored with a larger team including researchers at to Department of Energy National Labs SDS see the Texas Advanced

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00:03:50.520 --> 00:04:00.000
Amy Friedlander: Computing Center and records University and titled AI driven multi scale simulations eliminate mechanisms of SARS, Coby to spike dynamics.

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00:04:00.270 --> 00:04:14.220
Amy Friedlander: demonstrated the first all Adam simulation of the sorrows Cody to on below consisting of over 300 million animals, the paper around the 29 person author team. The first ACM Gordon Bell special prize.

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00:04:15.600 --> 00:04:23.340
Amy Friedlander: Research, which was announced in in November 20 20th super computing Romy I know you've had a busy day today.

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00:04:24.120 --> 00:04:39.870
Amy Friedlander: You've made a virtual trip to the UK and back again. So thank you so much for sharing your research with us today to my colleagues inside the building an app. Please join me in welcoming Dr. ROMEO tomorrow we will talk to us about the computational microscopy of the SARS Colby to

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00:04:41.760 --> 00:04:54.450
Rommie Amaro: Thank you. Thank you Amy for that Romy. Very good. Thank you for that very kind introduction. I am really so pleased and so honored to be able to to be invited to give this lecture to you all the seminar today.

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00:04:55.320 --> 00:05:02.970
Rommie Amaro: And I'm looking forward to telling you all about our work to use computational microscopy to explore the surface, Coby to virus.

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00:05:06.510 --> 00:05:20.640
Rommie Amaro: So some of you may have already heard about our work or read about our work in a very nice article that went to press in the New York Times in October. This was a beautiful beautifully laid out.

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00:05:21.900 --> 00:05:33.750
Rommie Amaro: Article that both in a digital form as well as an imprint for and I'm sort showing you to have those images here. And what this article did was it really showed the world.

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00:05:34.470 --> 00:05:45.690
Rommie Amaro: How much scientists have been able to learn about the stars, Coby to virus and its molecular piece parts and the model of the virus that we built and simulated as part of

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00:05:46.380 --> 00:05:55.770
Rommie Amaro: Our work with the National Science Foundation tremendous effort from this 30 number team that won the Gordon Bell prize was sort of really sort of featured prominently as part of this.

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00:05:56.610 --> 00:06:10.020
Rommie Amaro: As part of this article. And so what I'm going to do today is really trying to give to tell you the sort of the story behind these images the scientific sort of work that went behind making these beautiful images.

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00:06:11.460 --> 00:06:13.500
Rommie Amaro: But before I go there.

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00:06:14.580 --> 00:06:32.040
Rommie Amaro: I was also asked to give one slide about me or a little bit more of a personal reflection, perhaps on something that was important to me. And for this I of course you know there's, I have to say I feel so fortunate

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00:06:33.090 --> 00:06:36.450
Rommie Amaro: For so many different things that have happened in my career.

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00:06:38.040 --> 00:06:44.250
Rommie Amaro: There's one really sort of prominent figure is club Shelton who I'm showing here.

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00:06:45.780 --> 00:07:03.120
Rommie Amaro: And there's this beautiful quote from him. It says that says, My goal was to look with mathematical and computational means at the inside of cells one Adam at a time to decipher how living systems work. That is what I strive for. And I never deflected from that goal.

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00:07:04.140 --> 00:07:07.290
Rommie Amaro: I love that quote from him because it's really

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00:07:08.460 --> 00:07:18.150
Rommie Amaro: It's so him. It's so close, you know, close was to me a mentor a collaborator, a friend and really a kindred spirit and

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00:07:19.260 --> 00:07:24.510
Rommie Amaro: You know, I think part of what was so meaningful about knowing Klaus

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00:07:25.560 --> 00:07:33.990
Rommie Amaro: Was this at the end of this quote this, you know, not deflecting from the goal. And I have to say, you know, the simulation of large systems, as I'll describe today.

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00:07:35.520 --> 00:07:42.780
Rommie Amaro: For class in particular, you know, took really an enormous amount of perseverance, not only because it's scientifically difficult

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00:07:44.010 --> 00:07:58.110
Rommie Amaro: Not only because it's technically challenging you know how one constructs and simulates and analyzes these like huge data sets. I mean you quickly you quickly break all of the machines and all of the programs that you know used to work for smaller scale things

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00:07:59.490 --> 00:08:03.240
Rommie Amaro: You know, but also one of the hardest parts, too, is just culturally

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00:08:03.840 --> 00:08:14.670
Rommie Amaro: In terms of you know that most physicists biologists chemists, you know, recognizing that this work is highly interdisciplinary but most scientists in general tend to be reductionist in their approaches.

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00:08:15.000 --> 00:08:26.040
Rommie Amaro: Certainly at the molecular level, just by design. And there's a resistance to the simulation of big systems and, but, you know, Klaus persevered and I think it was oftentimes

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00:08:28.140 --> 00:08:30.240

Rommie Amaro: Hard one, you know, hard fought

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00:08:31.950 --> 00:08:48.480
Rommie Amaro: And you know, when I saw to do the same with influenza, which I'll just touch on briefly today, Klaus of someone who went from being a mentor to really being an ally and, you know, it's so important to have allies in no matter what your career is, I think,

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00:08:49.500 --> 00:09:05.070
Rommie Amaro: Particularly in science. And for me, he was really one of the one of the most important that I've been so fortunate to work with and you know he died suddenly unexpectedly in 2016 that was right around the time that my own independent lab was really hitting its stride.

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00:09:06.510 --> 00:09:19.350
Rommie Amaro: And that was a very difficult loss. It was a big loss for the community. It was you know personally also very difficult, but you know, I'm so pleased to be able to carry on his legacy and his vision and

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00:09:20.400 --> 00:09:29.760
Rommie Amaro: You know, I think the work that I'm going to tell you about today. And the combination of these partway of that of this work, winning the Gordon Bell special prize for

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00:09:32.220 --> 00:09:32.640
Rommie Amaro: You know,

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00:09:33.930 --> 00:09:46.110
Rommie Amaro: That was, you know, really very special and it was something that, you know, probably folks won't be too surprised to learn that you know we dedicated the work in the winter clothes. So with that,

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00:09:49.650 --> 00:09:50.550
Rommie Amaro: So, you know, one of

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00:09:51.750 --> 00:09:57.510
Rommie Amaro: Houses central things was this idea, this concept that one could use

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00:09:58.560 --> 00:10:08.520
Rommie Amaro: Mathematical models together with physics and chemistry and computing to explore those atomic movements of complex biological systems.

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00:10:09.570 --> 00:10:19.980
Rommie Amaro: In ways that evade experimental characterization to infect us molecular dynamics simulations as what he likes to call a computational microscope.

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00:10:20.430 --> 00:10:24.900
Rommie Amaro: And personally, I love that analogy because that's exactly how we intend to use this

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00:10:25.470 --> 00:10:34.980
Rommie Amaro: What we do is we can combine data sources coming from multiple types of experimental methods, many types of experimental methods.

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00:10:35.340 --> 00:10:50.850
Rommie Amaro: To develop data centric highly detailed data centric models of complex systems. So we can combine structural data multiple types of structural data techniques such as cry electron microscopy x ray crystallography and tomography.

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00:10:51.390 --> 00:11:01.440
Rommie Amaro: And together with mass spec data genomic data so that we can integrate faithful information about comix with the dynamics and the genomics and the system.

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00:11:02.100 --> 00:11:10.830
Rommie Amaro: And what then we're doing is we build these highly detailed atomic level models and then we're approximating

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00:11:11.610 --> 00:11:17.190
Rommie Amaro: That system down to its many atoms. And so all we're doing is defining a potential function.

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00:11:17.730 --> 00:11:25.050
Rommie Amaro: That shown here. And this basically describes the interactions that all the particles or the atoms in our system have with each other.

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00:11:25.620 --> 00:11:37.050
Rommie Amaro: And then we're simply integrating Newton's equation of motion over time. And so we're, you know, exploring the classical dynamics of the molecular piece parts of these systems.

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00:11:37.470 --> 00:11:54.810
Rommie Amaro: And we perform this numerical integration millions and billions and trillions of times in order to build up a dynamical understanding of our system over time. And we do this numerical integration, importantly, you know, these are really computationally intensive

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00:11:55.860 --> 00:12:03.810
Rommie Amaro: Methods and so they require big computers. And so, you know, the work that I'll tell you about today. We were very, very fortunate to be

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00:12:04.380 --> 00:12:20.250
Rommie Amaro: Really fantastically supported by a number of supercomputing sites including San Diego Supercomputing Center, including tak the front Tara machine and particular Dance, dance, Dion being just tremendously important in these efforts and also summit.

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00:12:22.140 --> 00:12:28.020
Rommie Amaro: at Oakridge national lab for some of the sort of larger scale systems that were running also very important.

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00:12:28.740 --> 00:12:38.220
Rommie Amaro: And so what I hope to tell you about today is how we've used these data centric computational simulations to go beyond what we know with experimental methods for source code to

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00:12:39.960 --> 00:12:55.140
Rommie Amaro: And so, so, you know, until about the February of last year, my, my lab, the research in my group, we had been focused for a number of years in trying in studying the influenza virus and the glycoproteins glycoproteins and so

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00:12:55.890 --> 00:13:02.520
Rommie Amaro: You know, last February, was a really sort of a special month for us because it was it was when

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00:13:03.000 --> 00:13:17.250
Rommie Amaro: This really massive effort that my group had developed over a period of about six years or so, starting in in 2013 working then with Klaus with his ally ship, as I mentioned,

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00:13:18.030 --> 00:13:30.450
Rommie Amaro: But then carrying across a number of years. We finally published that work and this this work was published in ACS central science. It was featured on the cover and this presented at the time. What was really one of the largest biophysical simulations.

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00:13:30.960 --> 00:13:41.610
Rommie Amaro: That had been sort of really studied scientifically and so it had about 160 million items and we were so proud to finally get that out, but it was around that time that you know

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00:13:42.270 --> 00:13:50.790
Rommie Amaro: That stars, Coby to started to catch our attention and, you know, back in February. So what I'm showing here, the total confirmed coven 19 cases.

74
00:13:51.240 --> 00:14:01.140
Rommie Amaro: As a log scale as a function of time for the early months of the pandemic from January through mid May of 2020 and then case counts in different countries.

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00:14:01.680 --> 00:14:06.630
Rommie Amaro: And so at that time, the United States and mid February the case counts were still very low.

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00:14:07.380 --> 00:14:13.710
Rommie Amaro: You know, maybe we had about a dozen or so, but we knew that the virus had already escaped mainland China. We knew that

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00:14:14.190 --> 00:14:27.240
Rommie Amaro: It had already started to look very bleak in the Lombardi region of Italy. And so, so this is when we started to really pay more attention, at least, you know, put in my group to this virus.

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00:14:28.560 --> 00:14:42.360
Rommie Amaro: And again, that same week was a very important week. This was on February 15 something else really sort of monumental happened and that was that the group of Jason McClellan at the University of Texas, Austin, together with collaborators at the National Institutes of Health.

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00:14:43.830 --> 00:14:54.900
Rommie Amaro: Were able, with a POP POP deposited into the bio archive. The first cry electron microscope structure so near atomic level structure of the stars, Coby to spike protein.

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00:14:55.590 --> 00:15:05.280
Rommie Amaro: And the day that structure dropped into the vital archive and this is paper dropped into the bio archive was when the we really pivoted our efforts to source code to

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00:15:06.270 --> 00:15:21.870
Rommie Amaro: And, you know, in general, just as a general comment. I'll circle back to this later. You know, the pre print servers, such as by archive archive archive have really played an important role in scientists ability to to really deliver

82
00:15:23.100 --> 00:15:30.570
Rommie Amaro: Enormous learnings and you know you know in throughout this throughout this pandemic. And I think, you know, it's hard to imagine

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00:15:32.250 --> 00:15:44.340
Rommie Amaro: You know, in some ways, it's very difficult to at once grapple with the enormous devastation that this disease has caused, which is just, you know, been really unconscionably definitely catastrophic

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00:15:45.810 --> 00:15:54.390
Rommie Amaro: On balance, at the same time with trying to find sort of silver linings from this pandemic and i think you know the the response of the scientific community being so strong and

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00:15:55.320 --> 00:16:04.170
Rommie Amaro: The formulation of new ways to collaborate and so forth, which I'll also touch on towards the end of the talk, you know, has really been part of that and been very important to the work that I'm about to tell you about

86
00:16:06.120 --> 00:16:16.500
Rommie Amaro: Okay. And so this is sort of a timeline of our work over the last year and it's, I'm not going to go through every part of explaining the slide, but it's really just to

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00:16:18.480 --> 00:16:28.410

Rommie Amaro: sort of give you a sense for the pace and the complexity of the work that we sort of that we accomplished that we saw to accomplish it accomplished in the end.

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00:16:29.010 --> 00:16:39.420
Rommie Amaro: Starting from February 2020 when the first cry. We have images of the spy protein were made available, and then how quickly and rapidly we and collaborators, you know, took up this data.

89
00:16:39.930 --> 00:16:51.840
Rommie Amaro: And began to build on it and compute on it and to learn on it and to apply new AI methods and to not only look at the spike protein, but how the spike interacts with a stew and eventually to build the whole

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00:16:53.340 --> 00:17:02.610
Rommie Amaro: The whole viral envelope and so forth. And to get that successfully running. And this was, you know, something that if if if two years ago, you would have said that you would

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00:17:03.030 --> 00:17:19.590
Rommie Amaro: This would have been just unimaginable to think that anybody could have accomplished, and it was only possible because of just a tremendous sort of collaborative effort from a number of teams. So today, in today's talk. I'm just, I want to cover mainly sort of what are the scientific highlights

92
00:17:20.670 --> 00:17:36.780
Rommie Amaro: That we've been able to learn. So what's the new science that we've been able to learn for this virus and sort of and to give a sense for the type of advances that, you know, modern day computing supercomputing and and many related algorithms and allied fields can provide

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00:17:38.700 --> 00:17:48.000
Rommie Amaro: Okay. And so, and I'm sure all of you are familiar with the source code to virus as I'm showing here. This is an image from our group, this is

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00:17:49.440 --> 00:17:58.260
Rommie Amaro: The all one of the all Adam models that we've created. So this virus is a lipid envelope virus. It looks just sort of like a golf ball with Spike sticking out of it.

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00:17:58.890 --> 00:18:02.280
Rommie Amaro: And these spikes are, in fact, called the spike protein.

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00:18:03.000 --> 00:18:13.590
Rommie Amaro: Or the S protein and we and others are very, very interested in how this spike works because it is as you see it sits on the outside of the virus.

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00:18:13.830 --> 00:18:26.550
Rommie Amaro: And it's the first point of contact that the virus has with human cells. So understanding the initial infection events really hinges on being able to understand what's happening with this important

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00:18:27.360 --> 00:18:38.550
Rommie Amaro: Part of the viral machinery. On top of that, it's also highly antigenic and so maybe. In fact, some of you have already been have already gotten your first jobs. I got mine on Monday. And so, you know, the

99
00:18:40.260 --> 00:18:52.020
Rommie Amaro: All of the available vaccines that we currently have two of them are encoding for the RNA of this like protein. And then the third one by Johnson and Johnson also utilizes a spike as part of its contract.

100
00:18:53.670 --> 00:19:07.650
Rommie Amaro: So the stars, Coby to in initial infection. One of the really important parts that has to happen is that this spike protein has to interact with a tight with the receptor on the wholesale called Ace, two

101
00:19:08.130 --> 00:19:18.660
Rommie Amaro: S stands for angiotensin converting enzyme to. So this is a molecule that I'm showing here in yellow that sits on certain types of cells in our body and

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00:19:19.380 --> 00:19:26.070
Rommie Amaro: And this spike protein has evolved the ability to bind very tightly to this receptor.

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00:19:26.430 --> 00:19:37.380
Rommie Amaro: And it's this binding that happens or this handshake, if you will, that happens between the hotel and the virus that catalyze is essentially that really precipitates or initiates the infection process.

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00:19:37.920 --> 00:19:45.330
Rommie Amaro: And so, um, so in this talk, I'm going to come back. So I want to draw your attention to this light blue bit in the middle.

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00:19:45.750 --> 00:19:54.240
Rommie Amaro: This light blue bit is called the receptor binding domain. We also call that the RB D. This is part of the spike protein and

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00:19:54.660 --> 00:20:10.980
Rommie Amaro: We're going to keep coming back to that because this is the part of the spike protein that makes that contact with a stew. And so there's there's a lot of questions. You know, that are sort of of mechanistic interest in terms of, you know, this particular area.

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00:20:13.350 --> 00:20:23.730
Rommie Amaro: Okay. And so, like many others. We were very excited to see the structural data come from not only the group of Jason McClellan, who was first

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00:20:24.270 --> 00:20:30.480
Rommie Amaro: To provide that structure. The pre print that I pointed to earlier was published in mid March and science.

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00:20:31.320 --> 00:20:41.610
Rommie Amaro: And this this data was, you know, very, very important. It gave us the first look at the spike protein, the head of the spike protein. So the spike protein is a timer.

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00:20:41.940 --> 00:20:57.870
Rommie Amaro: And each programmer. So each part of this timer so it's like three pieces that come together to form this molecular machine each pro tumor has almost 1300 amino acid. So it's rather along structure. It's a big protein.

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00:20:58.950 --> 00:21:07.380
Rommie Amaro: And with crime electron microscopy, they can get a view of what they call the head region, which goes up until about 11 the first 1100 residues.

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00:21:07.980 --> 00:21:13.110
Rommie Amaro: This is what I'm showing here and Jason structure, they were able to resolve.

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00:21:13.590 --> 00:21:22.920
Rommie Amaro: This RB D that I told you about that receptor binding domain in in up or open confirmation. So you can see how this little green bit is sticking up

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00:21:23.580 --> 00:21:31.770
Rommie Amaro: A few weeks later, the also fantastic group of David VCR at the University of Washington published a study in cell.

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00:21:32.160 --> 00:21:44.400
Rommie Amaro: Which presented another structure of the source code V2 virus identical in some ways are very close, similar to the open shorter. They also that Jason had presented, but they also presented

116
00:21:45.090 --> 00:21:58.230
Rommie Amaro: A model of the closed spike protein that they were able to generate not from averaging but from symmetry. And so this also was very important to us. And so

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00:21:59.520 --> 00:22:11.910
Rommie Amaro: We took these two structures early on and you know in March and we, you know, the structures so cry. We have a fantastic technique for probably many of you know, it won the Nobel Prize in Chemistry in 2017

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00:22:13.500 --> 00:22:25.110
Rommie Amaro: And it's just really sort of they say the, the resolution revolution because it's really been a game changer a truly transformative technology for the acquisition of

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00:22:26.100 --> 00:22:33.630
Rommie Amaro: biological structures, particularly those that are large and complex and have otherwise until now, been in counter trend to x ray crystallography.

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00:22:34.560 --> 00:22:39.240
Rommie Amaro: But as powerful as this technique is there are still things that it cannot see.

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00:22:40.020 --> 00:22:50.220
Rommie Amaro: And this is what we want to do with computing. We want to sort of give more insight into the bits that they cannot see with experiment. And this is, I think this beautiful synergy that exists.

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00:22:50.910 --> 00:22:54.960
Rommie Amaro: At this interdisciplinary interface between experimental science.

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00:22:55.350 --> 00:23:04.080
Rommie Amaro: And computational science, but also, together with physics and chemistry and biology and math. You know, it's really sort of, it's this, to me, that's one of the most fantastic parts.

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00:23:04.320 --> 00:23:09.540
Rommie Amaro: And I'll try to focus on the scientific message. I'll get back to it, but it's really sort of existing at this interface which is

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00:23:10.740 --> 00:23:16.530
Rommie Amaro: Difficult to pinpoint, you know, difficult to pigeonhole but it's still so important for biological discovery.

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00:23:17.850 --> 00:23:33.450
Rommie Amaro: Okay, so we modeled the the bits that they can't see we modeled using sort of different methods sort of standard methods. So we built in those missing loops and we were able to complete or provide sort of complete structures of the up of the RV up end of the RPG down states.

127
00:23:34.770 --> 00:23:39.600
Rommie Amaro: So, but we wanted to, you know, we, we really wanted to do was to

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00:23:41.130 --> 00:23:47.280
Rommie Amaro: We wanted to build in from the beginning. We wanted to build the whole virus and we wanted to understand how we're all those pieces coming together.

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00:23:47.610 --> 00:23:52.560
Rommie Amaro: But, um, you know, the way to do that. You don't just start with the whole virus, but you actually have to

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00:23:53.070 --> 00:23:58.770
Rommie Amaro: You know, you sort of you make models of the individual piece parts of that of the virus, you make sure that each model.

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00:23:59.220 --> 00:24:05.220
Rommie Amaro: Is good and experimentally validated and then you bring all those pieces together into the working whole

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00:24:05.700 --> 00:24:16.500
Rommie Amaro: So part of that was starting with the head so so we started with the spike protein first because this is where the data was and we knew that it was important for infection and as an antigenic component of vaccines.

133
00:24:17.790 --> 00:24:26.130
Rommie Amaro: So we started with the head which we got from the cry. We am the head structure. But then there are other parts of this spike protein.

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00:24:26.640 --> 00:24:37.980
Rommie Amaro: That I told you that they can't resolve because they move too much there to flexible. So part of what primarily I'm really has trouble seeing is, if the bits of the molecules are moving around too much, it can't get a clear image.

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00:24:38.730 --> 00:24:45.270
Rommie Amaro: For those parts so that includes the so called stock domain, as well as the trans membrane domain.

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00:24:46.260 --> 00:24:54.540
Rommie Amaro: And this little bit that sticks inside of the viral particle on the inside of the virus called the side of plasma tail which I'm showing here a purple.

137
00:24:55.020 --> 00:25:02.160
Rommie Amaro: So we put all these pieces we generated each of these sort of different these these additional parts that they couldn't see experimentally.

138
00:25:02.460 --> 00:25:10.050
Rommie Amaro: And we generated in the end this full length structure. So where we have all of the different domains fully represented throughout the whole spike protein.

139
00:25:11.850 --> 00:25:16.140
Rommie Amaro: The other thing that they can't see in cry. We are glycans

140
00:25:16.740 --> 00:25:27.720
Rommie Amaro: And you know glycans are very important post translational modifications. They happen to many different proteins they are particularly important for viral proteins.

141
00:25:28.110 --> 00:25:40.350
Rommie Amaro: And these are called. You know, and these are typically an old linked glycans so their post translational modifications that where there's an attachment that happens on either Syrian or three mean or disparaging and

142
00:25:41.190 --> 00:25:48.990
Rommie Amaro: It sort of decorates the certain residues of the protein gets sort of this extra decoration. This extra flourish.

143
00:25:49.380 --> 00:25:59.070
Rommie Amaro: Of sugar or glycans and so there's there's several different types of sort of sugar whities that come off of these and it literally, if you look at this, it's sort of looks like ornaments on a Christmas tree.

144
00:25:59.910 --> 00:26:12.930
Rommie Amaro: But we were able to rebuild the atomic level structure of these glycans of the sugar molecules using the data from glad comics.

145
00:26:13.920 --> 00:26:25.560
Rommie Amaro: We used initially the data from Max Crispin at the University of Southampton, the UK, together with Jason they provided this beautiful study that gave the molecular recipe for

146
00:26:25.620 --> 00:26:26.730
Amy Friedlander: Each one of these

147
00:26:27.030 --> 00:26:32.370
Rommie Amaro: Glycol protein. Each one of these like insights. So they were able to determine what the composition of those sites should be

148
00:26:32.910 --> 00:26:42.690
Rommie Amaro: Also PARIS, DO IS A Azadi at the University of Georgia. She also provided useful data here. And so you can see sort of all the different components that we built in.

149
00:26:43.380 --> 00:26:53.280
Rommie Amaro: Which is to give you a little bit of a closer look. And this is really an eye chart but so you have all of the complexity of the protein structure. There's some 1300 residues programmer.

150
00:26:54.210 --> 00:27:04.080
Rommie Amaro: But then at some of these disparate jeans and in fact there's 22 and link likens and to old link like and so at 24 times three.

151
00:27:04.560 --> 00:27:21.210
Rommie Amaro: Different sites on the spike protein, you have this extra bit this sugar. And you can see that their branch sugars. They have different types. And so they have different compositions different linkages. And so this was the hard work. This was really hard work for us.

152
00:27:22.230 --> 00:27:34.740
Rommie Amaro: In March in April in May, making sure that this was faithfully built and that you know every atom is

correct because you know we're building these are atomic level models and so

153
00:27:35.940 --> 00:27:49.350
Rommie Amaro: You have to worry about the chemistry and you have to worry about. It's like you have all of these little decisions that have to be made tight ration states and so forth. And we're going to bring them together and sort of a holistic picture it's

154
00:27:50.730 --> 00:27:59.310
Rommie Amaro: You know, they say the devil is in the details and this is certainly a place where it does get very detailed indeed so so for each of these timers, you have this sort of extra

155
00:28:00.090 --> 00:28:03.450
Rommie Amaro: Bit on the spike that are simulations contained

156
00:28:04.320 --> 00:28:12.840
Rommie Amaro: Now, we also need to take care of the membrane. And so the this this virus bugs off of the endoplasmic reticulum in the ER gold G intermediate compartment.

157
00:28:13.140 --> 00:28:21.450
Rommie Amaro: And thanks to many years of fundamental biological research, we know that the sort of the limited composition of these different membranes.

158
00:28:22.140 --> 00:28:40.410
Rommie Amaro: You know in in humans. And so we modeled our viral membrane off of what was known. And so this is the molecular composition, the ratios of different lipids, including cholesterol that are contained in our viral membrane.

159
00:28:41.970 --> 00:28:48.990
Rommie Amaro: And so what I'm showing now is just, we're looking at the bottom part of the spike protein. So this is about. And part of the spike.

160
00:28:49.440 --> 00:28:58.410
Rommie Amaro: The slab across the middle is the membrane. And you can see the different different limits here. We're coloring those and pink and yellow and red and orange. And so you can see how. They're all intermixed

161
00:28:58.860 --> 00:29:05.820
Rommie Amaro: But one more thing I want to draw your attention to is this highlighted bit in the middle. So you can see the protein is shown and gray ribbon.

162
00:29:06.120 --> 00:29:09.810
Rommie Amaro: And you have this bit this sort of going through the membrane that's a trans membrane part

163
00:29:10.260 --> 00:29:16.320

Rommie Amaro: But then, and this there's this tale that sticks into the inside of the virus and it has a whole bunch of 16 residues.

164
00:29:16.800 --> 00:29:22.980
Rommie Amaro: And not only that, but the system residues have another type of post translational modification. They are pull middle aged

165
00:29:23.280 --> 00:29:28.830
Rommie Amaro: And so these are basically alphabetic or greasy groups that are shown here, they look almost like little caterpillar's

166
00:29:29.070 --> 00:29:39.030
Rommie Amaro: And they're sort of the snorkel up into the membrane and they help to anchor these viral proteins in the membrane. So our model has that too. We tried to make it as complete as we possibly could.

167
00:29:39.300 --> 00:29:49.140
Rommie Amaro: Given the information that we have. And so this is what we built at the end of the day, we have the full length end to end spike protein with all of the domains.

168
00:29:49.740 --> 00:29:57.060
Rommie Amaro: We have simulated it in multiple states, we have the OBD upstate that I told you about. We also have the downstate

169
00:29:57.570 --> 00:30:12.510
Rommie Amaro: We have all the glycans and you can see how many glycans there are how it sort of decorates the entire end to end structure, we have the membrane with a different lipids and the poem elated sustains and this is what the fully reconstructed system actually looks like.

170
00:30:14.010 --> 00:30:26.070
Rommie Amaro: And then we sort of we we simulate it. Right. And so we start to see how these atoms move and how they wiggle and jewel and you know like Simon Says like all of

171
00:30:26.430 --> 00:30:34.230
Rommie Amaro: Everything can be understood at the end of the day, in terms of the wiggling and juggling of atoms. And so this sort of in the spirit of these methods, but I want to emphasize something

172
00:30:35.130 --> 00:30:48.570
Rommie Amaro: This is more than just graphics. These are more than just pretty pictures and it's not a video game right these are molecular dynamics simulations. This is numerical statistical mechanics.

173
00:30:49.080 --> 00:31:00.480
Rommie Amaro: And so what that means is that the trajectories or the this motion that we're predicting is done in accordance with rigorous theoretical laws.

174
00:31:01.710 --> 00:31:13.380
Rommie Amaro: To of course to some approximation. But what's powerful about this is that it allows us to extract from these microscopic properties we can extract back out.

175
00:31:14.070 --> 00:31:21.150
Rommie Amaro: Macroscopic experimentally testable predictions and that's what is the power of these approaches.

176
00:31:21.540 --> 00:31:34.590
Rommie Amaro: That it is not making pretty pictures, but it is actually giving us information that we can turn to our experimental collaborators with new hypotheses and and and she can help drive science forward.

177
00:31:35.190 --> 00:31:45.090
Rommie Amaro: And so, so these simulations that we ran they had, as I told you, multiple states we had 1.7 million atoms and these initial Spike Spike protein simulations.

178
00:31:45.540 --> 00:31:54.870
Rommie Amaro: We have water molecules there and sort of ions in the buffer, but I don't show you that. Because if I show you all the water. You can see the protein, and most people are interested to see the protein. So we're hiding all those waters.

179
00:31:55.500 --> 00:32:02.280
Rommie Amaro: For this work we were able to use we use the term 36 force field using MD to on Frontera and we ran

180
00:32:02.910 --> 00:32:17.850
Rommie Amaro: 256 nodes. So one of these simulations is sort of you know math is parallelized spatially decompose to run very efficiently over, you know, a set of nodes on on each of these architectures and we were able to get 16 as I can. Today,

181
00:32:18.630 --> 00:32:24.780
Rommie Amaro: So we ran for some amount of time, we were able together about four microseconds of data for each system. And what did we learn

182
00:32:25.800 --> 00:32:30.540
Rommie Amaro: Well, one of the first things that we learned, which is really, I think, so exciting was

183
00:32:31.020 --> 00:32:42.780
Rommie Amaro: We showed people what the spike the full length bully glycol isolated spy protein actually looked like and so on the left. What I'm showing is a picture of the spike protein.

184
00:32:43.170 --> 00:32:52.230
Rommie Amaro: But just showing the protein. And essentially, this is what cryo electron microscopy sees it sees the protein. And that is, of course, super valuable.

185
00:32:52.650 --> 00:33:05.070
Rommie Amaro: But it doesn't tell us the whole picture. So on the right you can see the dark blue bits are those glycans. And so you can see how different the spike protein looks

186
00:33:05.580 --> 00:33:16.860
Rommie Amaro: If you could see those sugars. And, um, you know, it's not only. So what I'm showing here. Each of those blue puffballs a little like toughs of fuzz.

187
00:33:17.370 --> 00:33:29.580
Rommie Amaro: That's the composite image of one particular glycan and sort of like looking at its snapshot over a microsecond of dynamics. And so what what becomes so clear, is how these glycans

188
00:33:30.420 --> 00:33:41.940
Rommie Amaro: In their in their ordinary dynamics at the small scale, they will. They're very, very flexible and they will sweep over large regions of the protein and literally create a shield

189
00:33:42.540 --> 00:33:50.880
Rommie Amaro: And why this is so valuable is because for the virus perspective is because, you know, our human cells also have sugars on them.

190
00:33:51.300 --> 00:34:03.960
Rommie Amaro: And so these viruses have evolved the ability to mask themselves or hide themselves with these very same sugars that our human body has. And in doing so, when the viruses inside of our system.

191
00:34:04.740 --> 00:34:14.100
Rommie Amaro: It's it's hiding. It's doing a tremendously good job at hiding this viral spike protein, which if the immune system could just see the protein.

192
00:34:14.340 --> 00:34:23.190
Rommie Amaro: It would be able to recognize it as a foreign antigen and go after and attack it. But when it's hidden under sugars. It's much, much harder for that to do for that to happen.

193
00:34:24.150 --> 00:34:28.920
Rommie Amaro: So this was this was really cool to see. So, you know, this was well received.

194
00:34:29.610 --> 00:34:36.960
Rommie Amaro: And also just say, you know, it's not only where the sugars are, but where the sugars aren't because if we know where the sugars are not we can think about

195
00:34:37.740 --> 00:34:48.480
Rommie Amaro: You know how to design novel drugs, for example, that could bind into these sites or it could be informative for future vaccine design. So there's all sorts of like Fallout from this knowledge.

196
00:34:50.550 --> 00:35:01.170
Rommie Amaro: Our simulations also showed why the spike has this upstate and the downstate so until we came along, you know, people saw those the upstate and the downstate

197
00:35:01.680 --> 00:35:06.090
Rommie Amaro: But there was no explanation for really why this movement had to occur.

198
00:35:06.600 --> 00:35:21.840
Rommie Amaro: But when one thinks about the sugars, you see. So clearly why this protein has to undergo these transitions. And that's because if you look at the close date. So I'm showing the clothes spike on top, looking like down at the barrel of the spike.

199
00:35:22.980 --> 00:35:34.020
Rommie Amaro: And then on the right, which I'm showing the open state the close date. You can see how effectively the spike protein uses those glycans are those sugars.

200
00:35:34.380 --> 00:35:48.900
Rommie Amaro: To hide part of the protein that are BD that receptor binding domain, you don't see it very well at all. You can see tiny bits of it but you mostly don't see it. And that's the part that needs to make that handshake.

201
00:35:49.800 --> 00:36:00.540
Rommie Amaro: But in contrast, look at the open spike with the open spike in that upstate you see a totally different picture of the OBD it's completely exposed and

202
00:36:01.980 --> 00:36:11.340
Rommie Amaro: This is the bit that needs to make that handshake. So we would say instead of calling this up and down if it could have known about the sugars at the time when they were first naming

203
00:36:11.760 --> 00:36:23.220
Rommie Amaro: They would have called it a defending Mode and an attacking mode or a shielded mode and unexposed mode, you know, but these are the type of things that we learn over time.

204
00:36:23.700 --> 00:36:33.870
Rommie Amaro: So this was this was also sort of very nice result. Of course, this. It's like these are at the end of the day when we run the simulations we have we save. Basically what we call trajectories are those

205
00:36:34.260 --> 00:36:44.340
Rommie Amaro: Iterative those iterated atomic level positions are integrated atomic level positions over time. And so it's just like enormously rich data sets.

206
00:36:44.850 --> 00:36:54.060
Rommie Amaro: And there's so many ways that they can be analyzed. So one of the first things that we did was really sort of look at what we call the accessible surface area. So we wanted to basically quantify.

207
00:36:55.110 --> 00:37:02.400
Rommie Amaro: The how much of the viral proteins surface was actually exposed at any given time, and how much was sort of shielded

208
00:37:02.880 --> 00:37:09.900
Rommie Amaro: And we did that you over various programs di. Okay. And the reason why we look at different programs, it is because

209
00:37:10.500 --> 00:37:21.300
Rommie Amaro: If you are, for example, a water molecule, your small right and it's going to be much easier for you to access these little crevices. You know, you, you're more nimble in that sense.

210
00:37:22.650 --> 00:37:33.660
Rommie Amaro: Larger molecules such as antibodies, it's a different story. You know, they're going to have, they're going to need larger patches to interact with. And so, you know, understanding what are sort of these average properties.

211
00:37:34.770 --> 00:37:43.050
Rommie Amaro: For these different components to for binding, you know, is something that, that the simulations can also have also provided

212
00:37:43.620 --> 00:37:55.440
Rommie Amaro: We did that for the head and we also looked at the stock and why we care about the stock is because the stock is among the most conserved bits of the spike protein. If you look across the beta coronavirus family.

213
00:37:56.400 --> 00:38:06.360
Rommie Amaro: You know, in other viruses. It's one of the places that people are currently looking to to develop broadly neutralizing antibodies or, you know, so called universal vaccines.

214
00:38:06.720 --> 00:38:15.360
Rommie Amaro: So there's a lot of potential there. But what you could see here is that this is very well shielded. And so this degree of shielding could hamper. You know, those, those efforts, although

215
00:38:17.850 --> 00:38:26.820
Rommie Amaro: You know there are moments where you know there is exposure and so forth. And so, but these simulations can help us understand understand these sorts of features.

216
00:38:28.650 --> 00:38:35.880
Rommie Amaro: The other sort of thing that we can do with this types of simulations, of course, that there's a lot of interest in is trying to take the structural information.

217
00:38:36.330 --> 00:38:45.660
Rommie Amaro: And also understand or map where the antibodies are binding, you know, so called neutralizing

antibodies and this is a rather old picture now there's been so many studies.

218
00:38:46.230 --> 00:38:51.240
Rommie Amaro: On where neutralizing antibodies are binding, but just to give you a sense for the kinds of things that one can do

219
00:38:51.720 --> 00:38:58.080
Rommie Amaro: We mapped on our structure. So the spike structure and white and the glycans are shown in dark blue

220
00:38:58.860 --> 00:39:08.820
Rommie Amaro: And then we mapped different types of antibodies. We mapped where they actually bind to the structure. So there's a whole bunch of neutralizing antibodies that bind that our BD in the upstate

221
00:39:09.180 --> 00:39:20.250
Rommie Amaro: So there's be 38 antibody 47 D 11. These are receptor binding domain and advisors, a lot of those there's an antibody that sort of very interesting. It says cryptic antibody 302 to

222
00:39:20.520 --> 00:39:30.630
Rommie Amaro: This actually vines in sort of the underside of the RB. And in fact, one would need multiple of those RBS to be open to gain access to that site.

223
00:39:31.320 --> 00:39:45.480
Rommie Amaro: We now know that the N terminal domain which sits sort of adjacent to the OBD is also a super energetic site lot of antibodies targeting the the N terminal domain, one of the first examples was 48 that I'm showing here.

224
00:39:48.450 --> 00:39:54.750
Rommie Amaro: But so, so this was the shielding and there's there's a lot that's interesting about shielding and that's typically how people

225
00:39:55.620 --> 00:40:00.600
Rommie Amaro: Until now really have thought about glycans but we noticed something else.

226
00:40:01.080 --> 00:40:13.650
Rommie Amaro: And we noticed something very interesting that, and this was, I have to say, a wonderful collaboration with Lisa five major universities in Dublin. She is a fantastic like a biologist, like a chemist and you know as

227
00:40:14.670 --> 00:40:17.790
Rommie Amaro: You know we early on in this pandemic.

228
00:40:18.960 --> 00:40:27.300
Rommie Amaro: I'll talk about this more at the end. But, you know, we realized how much we needed to collaborate with other scientists and

229
00:40:28.440 --> 00:40:31.500
Rommie Amaro: She was one who was really important for us. One particular collaborator.

230
00:40:32.190 --> 00:40:39.030
Rommie Amaro: But we realized when we were building this by protein, something we noticed was that when we built the closed protein.

231
00:40:39.300 --> 00:40:50.550
Rommie Amaro: What we saw was that this one particular glycogen deposition and to 34 was sort of always sticking out in solution. Okay. So it was always sort of sticking out words in the close date.

232
00:40:51.210 --> 00:41:02.340
Rommie Amaro: When the when we looked at the open state. What we noticed was that the glycan that perfect like and was sticking out in two of the chains, but in one of the change. It was sticking in

233
00:41:03.510 --> 00:41:13.170
Rommie Amaro: And so we took a closer look. And we realized that when we rebuilt the glycan side chain. So as I mentioned,

234
00:41:13.620 --> 00:41:22.170
Rommie Amaro: Crime em, they can see the protein. And so I'm showing here in red surface and gray and blue. That's the spike protein, we're looking at the top head.

235
00:41:22.710 --> 00:41:32.430
Rommie Amaro: This is that receptor binding domain. The crowd electron microscopy can see the first sugar unit here. This is a good snack. In this case, they can see that in dark blue I show

236
00:41:32.880 --> 00:41:47.910
Rommie Amaro: In green is what we built in. And when we built that sugar side chain using simulation, what we saw was that it filled up the void space that was made when this our BD lifted up.

237
00:41:48.720 --> 00:41:59.250
Rommie Amaro: And so this was very curious to us and we said, Well, what if, what if we delete those what if we invite delete. You know, I'm thinking like computational person I say delete.

238
00:41:59.850 --> 00:42:11.850
Rommie Amaro: Biology, we say we could mutated we mutated we mutated. These two alanine. So if you make this disparaging analogy, and it's no longer going to be like oscillated so we eliminate the sugar at that residue.

239
00:42:12.870 --> 00:42:25.530
Rommie Amaro: And so we did that in silica first to see what would happen. And we saw what we saw was that this prediction that this binding domain is our BD when it doesn't have those sugars. There was going to collapse down

240
00:42:26.760 --> 00:42:37.050
Rommie Amaro: And then we called I called up, Jason McClellan, who I never collaborated with before and I figured he was very busy doing vaccine stuff because he's one of the co inventors of on the return of vaccine.

241
00:42:39.390 --> 00:42:44.940
Rommie Amaro: And I just said, Hey, would you, would you, we have this hypothesis about these two glycans

242
00:42:45.600 --> 00:42:51.930
Rommie Amaro: Sounds a little weird. But what do you think, and so he said he said he agreed to run the experiments. So he did those same mutations.

243
00:42:52.290 --> 00:43:02.700
Rommie Amaro: In the lab and he created an essay by layer interferometry essay that sort of looks at quantifies interaction between H2 and and the spike.

244
00:43:03.450 --> 00:43:13.050
Rommie Amaro: And what he saw substantiated. Our hypothesis was that in fact when you make these mutations. He did the single point mutations. But when you make these mutations, it reduces the ability

245
00:43:13.410 --> 00:43:21.780
Rommie Amaro: Of the site to interact with a two and our explanation of that mechanism is because it's actually when you remove that structural scaffold.

246
00:43:22.080 --> 00:43:37.710
Rommie Amaro: Though that RB collapses down and then becomes unavailable for binding a base to so that was really nice. This work was cool, because, you know, not only did we begin to understand this extensive shielding of this protein, but we showed for the first time.

247
00:43:39.330 --> 00:43:42.330
Rommie Amaro: For any viral protein that we know of, actually.

248
00:43:43.980 --> 00:43:54.330
Rommie Amaro: The new role for glycans in biomolecular systems. And that's it. They're actually what we showed was that these two glycans were actually participating

249
00:43:54.630 --> 00:44:00.930
Rommie Amaro: In the structural dynamics in the mechanism of the viral weaponry itself. And that was very cool.

250
00:44:01.470 --> 00:44:16.980
Rommie Amaro: So this work was published in a central science has been very, very well received and I think it's really providing sort of like a new a new insight into the biological phenomena essentially like of sugars, you know, their roles and their mechanisms in biology.

251
00:44:18.120 --> 00:44:22.560
Rommie Amaro: Very cool. Okay, so, but what else did we do so you know that that was just to start

252
00:44:23.910 --> 00:44:28.620
Rommie Amaro: So with standard or conventional molecular dynamics. One of the big challenges is that

253
00:44:29.340 --> 00:44:38.640
Rommie Amaro: You know, it's very informative. Like I just showed you where we can sort of use MD to sort of explore the baseline dynamics. I like to call it around particular states.

254
00:44:38.850 --> 00:44:45.000
Rommie Amaro: So we took their clothes state and we let it with a logical and we saw something and we took the open state and you know we did something else.

255
00:44:45.420 --> 00:44:56.790
Rommie Amaro: But if we want to actually see that functional transition of going from, closed, open, very, very, very hard with MD, especially for size that our systems that have this sort of size and complexity. So

256
00:44:57.570 --> 00:45:06.120
Rommie Amaro: We partner. So what you what happens in standard MD, is that you spend a lot of time waiting for things to happen you're running you're running you're running and you're waiting, waiting, waiting. I'm

257
00:45:06.870 --> 00:45:14.610
Rommie Amaro: Lillian Chung at the University of Pittsburgh became another collaborator of ours, she's developed this wonderful method called weighted ensemble molecular dynamics.

258
00:45:14.940 --> 00:45:27.420
Rommie Amaro: which focuses on trying to be more efficient in terms of simulating functional transitions and so you spend using her method. It allows us to spend much less time waiting

259
00:45:27.840 --> 00:45:44.280
Rommie Amaro: And actually do a better job going up these to these interesting places on the energy landscape which are accessible, you know, in sort of normal room temperature dynamics or body temperature dynamics, but they just, it's like a waiting game in terms of them happening.

260
00:45:45.480 --> 00:45:55.110
Rommie Amaro: And so we use her method we. It's called West Pa. It's a simulation program that has been she's been working on for a number of years.

261
00:45:55.560 --> 00:46:02.790
Rommie Amaro: We use that to study the opening of the receptor binding domain to go from the close to the open confirmation

262
00:46:03.480 --> 00:46:14.850
Rommie Amaro: And for this, we used a slightly truncated system model for the head. We didn't include the stock. We just had the head, which was still really large had 600,000 atoms. This is the biggest simulation that they

263
00:46:15.780 --> 00:46:22.950
Rommie Amaro: Largest most complex by a very large degree that they've used for this method. That's why we put a little crown on it here.

264
00:46:23.760 --> 00:46:35.010
Rommie Amaro: And we ran in this case, instead of using Frontera we used another machine at Texas, which is called Longhorn which is just a big GPU farm.

265
00:46:35.400 --> 00:46:45.540
Rommie Amaro: So we took over 100 of these Nvidia V 100 GPUs for several weeks and using her method, we were able to generate

266
00:46:45.810 --> 00:46:59.040
Rommie Amaro: Actually this is outdated now, but we were able to generate over 300 of these opening pathways and just to put this into perspective, if we wanted to use standard molecular dynamics or conventional classical molecular dynamics.

267
00:47:00.120 --> 00:47:19.380
Rommie Amaro: To see that opening it would have taken us on the order of 10 months to eight years using just conventional approaches. So you can see there's this would be, you know, going from just taking way too long to actually being tractable in a real in a sort of a realistic amount of time.

268
00:47:20.850 --> 00:47:30.420
Rommie Amaro: And so this is what we saw. So I froze it was in the last one to i don't know what's wrong with this guy, but I'll show there's another movie where we'll see it again.

269
00:47:31.320 --> 00:47:36.690
Rommie Amaro: But so we were able to sample that open that close to open transition

270
00:47:37.170 --> 00:47:49.380
Rommie Amaro: And that includes so why we care about this is that we get 300 of these opening pathways and now we can really sort of see what are the mechanisms, the atomic level mechanisms that this spike protein uses

271
00:47:49.950 --> 00:48:00.630
Rommie Amaro: To open. So there's like there's just tons of it's just it's, you know, part of what you know excites me as you can probably tell, and others. A lot of others, you know, is really sort of like

272
00:48:02.340 --> 00:48:08.190

Rommie Amaro: Understanding how these amazing molecular machines actually work. You know, how do they do all of these

273
00:48:08.520 --> 00:48:14.880
Rommie Amaro: Phenomenally interesting jobs, you know, in the cell. And so this is the kind of method that lets us see

274
00:48:15.240 --> 00:48:27.540
Rommie Amaro: Down to the many animals like how this is actually happening. And so we can do these detailed analysis of looking at salt bridges forming and hydrogen bonds forming and sort of like what's happening along the opening pathway.

275
00:48:28.770 --> 00:48:41.280
Rommie Amaro: And one of the really interesting things that we saw was another glycan which we initially didn't pay much attention to because when we just looked at the open and close states we didn't see anything particularly interesting about it.

276
00:48:42.030 --> 00:48:53.160
Rommie Amaro: But when we look at the opening pathway we saw that there was one glycan in particular and 343 now that actually acted like a gate.

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00:48:53.850 --> 00:49:02.280
Rommie Amaro: Initially this residue is sort of helping to cover and shield part of the OBD but then

278
00:49:03.090 --> 00:49:15.270
Rommie Amaro: Under just normal dynamics. There's no forces know perturbations. This guy starts to like do hand jiving with the other residues near it. And it lifts the RB up

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00:49:15.870 --> 00:49:23.040
Rommie Amaro: And so we went back to Jason and we said, we have another crazy hypothesis. And he said, well, let's test it and

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00:49:23.850 --> 00:49:36.690
Rommie Amaro: He they tested a whole bunch of different mutations that we predicted and showed actually that this 343 is even more important than the other two. In terms of governance, the other two that we had previously found glycans in terms of affecting

281
00:49:38.190 --> 00:49:43.620
Rommie Amaro: The, the confirmation or dynamics of the spike in particular the opening mechanism. So this is currently under review.

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00:49:45.420 --> 00:49:52.530
Rommie Amaro: Okay, and then going beyond. I'm sorry. I'm going to slow. I'm going to speed it up. I really well. So then, going beyond this, you know, we're interested in so many other things you can imagine.

283
00:49:54.390 --> 00:50:02.370
Rommie Amaro: We have simulated also the ACE to receptor and I'm showing that here in the membrane. And one of the really interesting things that we thought here was that as to

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00:50:03.450 --> 00:50:14.940
Rommie Amaro: Has an enormous degree of flexibility relative to the membrane. And this is something I don't think anybody expected to see, you know, we kind of always think about these proteins standing upright and being sort of very tidy and well behaved, but it's actually waving around

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00:50:15.780 --> 00:50:22.320
Rommie Amaro: Undergoing like a very large degree of tilt and it turns out we think that actually this sort of degree of till to helps to

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00:50:23.370 --> 00:50:28.680
Rommie Amaro: To facilitate sort of the all of the different mechanical changes that need to happen.

287
00:50:28.920 --> 00:50:41.130
Rommie Amaro: In order for the viral and host cell membranes diffuse because these proteins they start like this. But then there's this huge confirmation arrangement as the viral members views during the first part of infection. So what we did with

288
00:50:41.730 --> 00:50:49.500
Rommie Amaro: The weighted ensemble is actually get a picture of how this RV opens, you could see that opening. Finally, I'm sorry. My other movie didn't work.

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00:50:49.800 --> 00:50:55.320
Rommie Amaro: But once it's open, and in that position, it can then make contact with these two and we have simulations.

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00:50:56.070 --> 00:51:08.520
Rommie Amaro: That actually have this interaction of the two proteins across the two parallel membrane system we're really interested, of course, to look at the contact what's happening in here at this interface, but also there's so much else to see

291
00:51:09.360 --> 00:51:16.170
Rommie Amaro: There's an enormous degree of stock bending and here. One of the interesting things we did for the Gordon Bell was actually using AI driven

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00:51:16.530 --> 00:51:25.290
Rommie Amaro: Sort of multi scale approach to to learn dynamics from the weighted ensemble and from the conventional MD at the single protein scale.

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00:51:26.220 --> 00:51:32.640

Rommie Amaro: To then help drive confrontational sampling of these different molecules in larger and more complex scenes.

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00:51:32.970 --> 00:51:47.130
Rommie Amaro: Where we otherwise will be even more limited because of the increase in the number of atoms and the complexity of the landscape. So I don't talk about that much in terms of the technical details for the AI. There are some in the in the Gordon belt pre print

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00:51:49.200 --> 00:51:57.840
Rommie Amaro: But we're working to write that up. Now this was a great collaboration with Arvin ramen often at Argonne National Lab, together with Shanta new job at Rutgers

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00:51:59.310 --> 00:52:10.290
Rommie Amaro: But what we could see is really that there are these flexible hinges in the spike stock in particular, and this corroborated studies by Homer, as well as

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00:52:11.040 --> 00:52:27.870
Rommie Amaro: Martin Beck at the Max Planck that showed a large degree of tilting and cry electron tomography, and also simulation studies that they published last late last summer. And so we can use these approaches to try to, again, sort of sample. What's happening with these dynamics.

298
00:52:29.520 --> 00:52:40.770
Rommie Amaro: But then, you know, we've sort of we as we keep going. You know, we've also we've been very interested to develop models of the entire virus. And so, you know, the single biggest obstacle to

299
00:52:41.670 --> 00:52:55.740
Rommie Amaro: The simulation of structures at the scale is building a membrane that's good enough for simulation. And that's because of differences in the inner and outer leaflets of these membranes causes a lot of

300
00:52:56.670 --> 00:53:12.210
Rommie Amaro: Small issues to happen with the positioning of these atoms. And so, so we had to develop and intensive ITERATIVE SORT OF membrane remodeling process such that we could get everything

301
00:53:12.900 --> 00:53:18.180
Rommie Amaro: cooperating in some sense. So that is numerically stable when we go to simulate it and still biologically accurate.

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00:53:18.570 --> 00:53:25.110
Rommie Amaro: We were able to do this in time for the Gordon Bell submission and actually simulate the full viral envelope.

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00:53:26.010 --> 00:53:36.150
Rommie Amaro: At the with molecular dynamics simulations we did this pilot runs on Fonterra and then we move to Summit for production and we showed really nice scaling of the namby to code and

304
00:53:36.810 --> 00:53:42.960
Rommie Amaro: You know with this model now ready to go. It's like, it opens entirely new dimensions for studying viral infection.

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00:53:43.170 --> 00:53:52.020
Rommie Amaro: And therapeutics and also something which I don't have time to talk about, but I'm intensely interested in is an understanding elements of airborne transmissibility

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00:53:52.320 --> 00:54:00.990
Rommie Amaro: And what happens to these viruses when they're in aerosols and this is a place. Also, you know, the study of aerosols and the chemistry of aerosols.

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00:54:01.560 --> 00:54:09.960
Rommie Amaro: I realized chemistry is not one of the co sponsors of this seminar, but this is really integral is sort of like there are

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00:54:10.950 --> 00:54:20.760
Rommie Amaro: There's a lot of development to be done in terms of experimental methods that atmospheric chemistry and physical chemistry types need to develop and we're we're doing that now, hand in hand.

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00:54:21.540 --> 00:54:33.360
Rommie Amaro: With folks at various in various investments and other I guess portfolios and fantasy. But this is something else where I think simulation has a tremendous place where has it has a lot to give

310
00:54:34.740 --> 00:54:45.630
Rommie Amaro: Okay. And so I had to give a shout out to there was really just an incredible 30 almost 30 member team that participated in this these Gordon Bell activities which we you know we won a special prize Gordon Bell.

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00:54:47.430 --> 00:54:55.290
Rommie Amaro: Contest or press whatever in in November, which was really cool. And just like an incredible, incredible effort and of course it was.

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00:54:56.520 --> 00:55:07.920
Rommie Amaro: Sponsored by so much support from the National Science Foundation, and by tack and others. So it was really great. And this is also an international collaboration we also work with the UK for parts of this model, which was really important

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00:55:09.090 --> 00:55:12.450
Rommie Amaro: Okay. And then I think I'm probably like at a time. I've gone too long. I apologize for that.

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00:55:13.230 --> 00:55:22.380
Rommie Amaro: I didn't want to say, you know, the simulations also can give us the first glimpses of what happens to

these proteins when they undergo mutation. So, of course, there's been a lot of discussion about

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00:55:23.190 --> 00:55:39.990
Rommie Amaro: How these the spike protein and the virus in general is mutating as it circulates in these populations. And this is probably going to at some point cause real trouble for the current vaccines Madonna just announced yesterday they have you know put out a new potential variant.

316
00:55:42.030 --> 00:55:47.400
Rommie Amaro: formulation for the vaccine update to the vaccine for the South Africa variant and we can

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00:55:48.300 --> 00:55:57.900
Rommie Amaro: You know, use these computational methods to assess, sort of, what are the structural changes and to just to predict. You know, like how much we should potentially

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00:55:58.890 --> 00:56:05.940
Rommie Amaro: Need to be concerned for for different mutations, we're doing that. Also, and then I just want to say, you know, it's been such a special time to be a scientist.

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00:56:07.230 --> 00:56:07.950
Rommie Amaro: The

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00:56:09.030 --> 00:56:14.820
Rommie Amaro: Again, one of sort of like the silver linings of the bright spots of the pandemic, I think, has been just the tremendous response from the scientific community.

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00:56:15.600 --> 00:56:25.020
Rommie Amaro: Early on in the pandemic colleague in the UK Adrian Mulholland and I realized that it would if we needed to do something very different, you know, ordinarily, we would build these models.

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00:56:25.920 --> 00:56:39.870
Rommie Amaro: And our models and our simulations and we hold our scientists, we always hold our cards close to our chest because science rewards people being first. And so there's some degree of the incentive of the system being to not share

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00:56:40.980 --> 00:56:45.060
Rommie Amaro: But we realized that this was very different than anything that any of us had ever

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00:56:45.720 --> 00:56:51.720
Rommie Amaro: Confronted before and we would need to do something different in terms of how we operated as a scientific community and so

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00:56:52.470 --> 00:57:04.410
Rommie Amaro: In March, we drafted a set of principles that nearly every molecular simulation group in the world

committed to this included the use of pre print servers fair data.

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00:57:05.100 --> 00:57:14.790
Rommie Amaro: Sharing of systems and just all of that it led to the creation of the cover 19 molecular structure therapeutics hub, which is another NSF sponsored

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00:57:15.480 --> 00:57:24.180
Rommie Amaro: Term investment in molecular simulation this now has tons. It's like a clearinghouse for simulation data systems methods from all over the world.

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00:57:24.510 --> 00:57:33.570
Rommie Amaro: And anyone who's interested can, you know, can go there to grab models and complete to work on them and further embellish them and analyze them.

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00:57:33.900 --> 00:57:42.300
Rommie Amaro: And this is going to be, I think, a tremendous resource for AI driven methods in the space of source code to it's just the amount of data here. It's just remarkable.

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00:57:42.660 --> 00:57:53.730
Rommie Amaro: Our data set. For example, the sharing has been fantastic Rd to shut that the set that we made on Frontera has been shared over 4000 times by various academic groups industrial groups.

331
00:57:54.330 --> 00:58:02.790
Rommie Amaro: So we've been able to really sort of amplify the impact from this work, and I think that's been really great. I also just want to say you know how important it is

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00:58:03.330 --> 00:58:14.460
Rommie Amaro: That we have well developed community codes, you know, this is the hard work of people like Klaus and others who carry it forward, who have

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00:58:14.940 --> 00:58:18.120
Rommie Amaro: Ready at the ready for scientists to be responsive.

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00:58:18.480 --> 00:58:29.970
Rommie Amaro: These excellent codes that, you know, it requires it requires investment in these things, such that we're prepared to use them immediately as soon as you know, the next thing hits or hopefully in advance. Next time will be more prepared.

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00:58:30.510 --> 00:58:39.090
Rommie Amaro: But just want to emphasize, really, the importance of Community software and open access in this space. And then also, of course, the HTC Consortium for coven 19

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00:58:39.900 --> 00:58:54.540

Rommie Amaro: What a tremendous gift for scientists in the space, you know, ordinarily, it would take eight months to a year to get compute time one puts together a proposal, the proposal is reviewed, eventually it gets allocated.

337
00:58:55.650 --> 00:59:04.320
Rommie Amaro: In this for big simulations, like the whole virus that could take years it took us three years to get compute time for influenza after it was built and ready to go. We still couldn't get time

338
00:59:05.160 --> 00:59:17.280
Rommie Amaro: But we did eventually and that was great. And with stars Colby to however we you saw how quickly we got access to it. It was like that was amazing. And I think this has been sort of the, the whole mobilization the agility.

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00:59:17.790 --> 00:59:26.190
Rommie Amaro: Of the scientific community and kind of all aspects of that just really one of, again, one of the Silver Linings in the pandemic.

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00:59:27.420 --> 00:59:33.630
Rommie Amaro: With that, I will stop talking and we can have questions I hope I didn't go so long that we don't have time for questions.

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00:59:34.230 --> 00:59:46.350
Rommie Amaro: But I just wanted to thank the knowledge is. It's been, like I said, is a huge team with tremendous contributions so many sleepless nights so many pre prints. I mean, it's just like keeping pace with everything has been

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00:59:47.760 --> 00:59:54.900
Rommie Amaro: It's been, it's been difficult and exhausting, but also so exciting. And just fantastic at the same time. And so I just want to thank

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00:59:55.290 --> 01:00:14.850
Rommie Amaro: Also NSF for support early support on this project in multiple ways. You know MTB sponsored this as part of a rapid and also the compute infrastructure which is just some of the best in the world. So with that, thank you. And I'm happy to, you know, discuss and take questions.

344
01:00:16.320 --> 01:00:22.320
Amy Friedlander: Everybody. If you can find your symbols that indicate. APPLAUSE

345
01:00:24.030 --> 01:00:30.810
Amy Friedlander: So a couple things as Andrew pointed out chemistry is a co sponsor of this chemistry is

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01:00:30.810 --> 01:00:31.740
Rommie Amaro: Party. Yes.

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01:00:31.770 --> 01:00:33.930
Rommie Amaro: Ma'am. Sorry, sir. Yes.

348
01:00:35.040 --> 01:00:35.790
Rommie Amaro: I do that.

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01:00:35.850 --> 01:00:43.260
Amy Friedlander: Is with us from the chemistry division, so it's okay can't become our friends to um and

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01:00:43.800 --> 01:00:54.960
Amy Friedlander: I also want to acknowledge Alan test here and I believe Joanne tourneau from the director of biological sciences, who are co sponsors of this, as we said early on, but they are here and

351
01:00:55.260 --> 01:01:06.180
Amy Friedlander: Sorry, do you have a number of questions, and I believe we have 30 minutes for conversation and I get to mute and go dark because Andrew is going to lead off with the question. Carry on. Andrew

352
01:01:10.980 --> 01:01:11.790
Rommie Amaro: Well, you're muted.

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01:01:11.850 --> 01:01:13.080
Amy Friedlander: Andrew you're muted.

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01:01:15.420 --> 01:01:17.040
Amy Friedlander: Andrew the mute button is the hardest.

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01:01:17.040 --> 01:01:18.330
Andrew Lovinger: One. Thanks very much.

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01:01:18.480 --> 01:01:24.480
Andrew Lovinger: And really, this was a fascinating and inspiring lecture one of the very best. We have

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01:01:25.500 --> 01:01:36.570
Andrew Lovinger: So the first question folks about the holistic optimistic detailed simulations that you have provided, and the question arrow is Mr. Shea who is asking

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01:01:37.230 --> 01:01:48.330
Andrew Lovinger: Do you still think there is a role for researchers who take the more reductionist approach and still investigate coarse grained or multi scale approaches. So model scoring functions.

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01:01:48.570 --> 01:02:00.900
Andrew Lovinger: Or even AI and ML researchers that skip the molecular dynamics platform and instead employ other approaches to quickly get at the very structures, but who's out of time. Skin information.

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01:02:01.950 --> 01:02:09.570
Rommie Amaro: Yes, yes, yes, yes, and yes, there's so much room for for all these different methods, I think.

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01:02:10.920 --> 01:02:19.740
Rommie Amaro: I always say that it takes all types and all kinds. You know, I think it is still important, and I don't. I hope I don't give the wrong impression. I mean,

362
01:02:20.460 --> 01:02:32.490
Rommie Amaro: It is really important to develop these models for individual molecular piece parts and there's so much that can be done for each of those in so many different ways from so many dimensions with atoms or without atoms, you know,

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01:02:32.880 --> 01:02:43.650
Rommie Amaro: Different methods is marred also mentioned all which, you know, have the potential to play an important role in sort of catalyzing discovery and scientific knowledge around these targets.

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01:02:46.050 --> 01:02:51.420
Rommie Amaro: I do also believe, however, that, and I hope that our work will show that

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01:02:52.560 --> 01:03:02.460
Rommie Amaro: We need to do more than just look at each individual component valuable as that is, but to also understand how these components come together into the working hole.

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01:03:02.850 --> 01:03:11.220
Rommie Amaro: And to try to understand also sort of emergent behavior and there will be, you know, which is very difficult and will take different types of

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01:03:12.360 --> 01:03:19.380
Rommie Amaro: Not only experimental methods, but also simulation methods, different types of physics as you go across these different skills. I mean, even

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01:03:21.150 --> 01:03:27.720
Rommie Amaro: You know there's there's always like I i sort of liken it to like using a different lens. You know, you have these microscopes and you can change the lenses.

369
01:03:27.750 --> 01:03:39.690
Rommie Amaro: Are depending on what you need to see or want to see or the questions you're asking you change the lenses. That's just like it is with changing these different methods. I'm also really excited, of course, about the application of AI the intersection of AI.

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01:03:40.770 --> 01:03:50.160
Rommie Amaro: Together with the experiments and the simulation and sort of the because of the breadth of the studies that have been done now on so many of the targets and stars coke to I think it's going to be

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01:03:50.580 --> 01:03:57.990
Rommie Amaro: It has a potential in my opinion to be like a really great sort of driving use case for AI technology going forward.

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01:03:59.100 --> 01:04:00.600
Rommie Amaro: But we're going to have to see how that plays out.

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01:04:05.340 --> 01:04:08.340
Amy Friedlander: Okay so we are tag teaming the questions really

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01:04:09.060 --> 01:04:10.350
Rommie Amaro: Grow I'm going

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01:04:10.560 --> 01:04:22.500
Amy Friedlander: From Daniel Cox, have you focused on the urine binding domain which apparently also fluctuate substantially and and this is unresolved by cryo em.

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01:04:23.100 --> 01:04:42.540
Rommie Amaro: Yes, that darn fear and loop. There have been so many structures of the spike protein. They have resolved. Pretty much every loop on it by now except for that one, which is very tricky and very interesting we, you know, we're working on a lot of things with this protein.

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01:04:44.040 --> 01:04:58.680
Rommie Amaro: We aren't right. I have to say to be completely honest with you. We don't have a focused Fearon loop study, but we were sort of we're touching on it and contacting it sort of in different ways. Under trying to understand the dynamics of that area.

378
01:04:59.280 --> 01:05:02.850
Rommie Amaro: And how it might be correlated to other events.

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01:05:04.680 --> 01:05:12.060
Rommie Amaro: But it is certainly one where there is a lot of interest. And I think molecular simulation potentially has a lot to give because of the difficulties in

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01:05:13.470 --> 01:05:14.790
Rommie Amaro: You know in in determining

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01:05:15.900 --> 01:05:18.720
Rommie Amaro: High Resolution structures for that flexible region.

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01:05:19.920 --> 01:05:25.350

Rommie Amaro: I wish I had it, but I wish I had like a yes oh we're also doing this I don't for that particular area, but I hope that someone does

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01:05:28.650 --> 01:05:40.320
Andrew Lovinger: The next question is from Aranda Lynch. She's asking, why would the black and additions be so consistent and specific is the variability in the added glycan unit at a given guy constellation side.

384
01:05:41.580 --> 01:05:58.050
Rommie Amaro: Great question. Yes. So the glycans do have a. They do, they do very, you know, they call this micro heterogeneity different sites on a spike protein will have differing degrees of micro heterogeneity.

385
01:06:00.000 --> 01:06:11.190
Rommie Amaro: Interestingly, the, the, the glycans at for example position to 34 which I showed you at the beginning and which we hypothesize we're playing a role in the mechanism.

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01:06:12.480 --> 01:06:28.230
Rommie Amaro: That particular glycan is pretty well conserved. It's either a man eight or a man nine glycan they call it. And that was another clued us that the the conservation of that glycan type and also it's a little bit of a in some sense an unusual type

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01:06:29.070 --> 01:06:34.230
Rommie Amaro: That it was it was an indication that may be something else that it was also, you know, potentially doing something

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01:06:35.940 --> 01:06:42.390
Rommie Amaro: But you know, I would say to. So, this I would want to make another comment on like in micro heterogeneity. So, um,

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01:06:44.640 --> 01:06:54.780
Rommie Amaro: It is important, it's harder for us. People like me, you know, to molecular stimulators to get a really comprehensive picture of

390
01:06:55.260 --> 01:07:02.580
Rommie Amaro: Micro heterogeneity because of the Communist Oriel explosion. If you try to, you know, generate every single type of

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01:07:03.390 --> 01:07:06.900
Rommie Amaro: Combination you know you have way too many models and it's just computationally intractable.

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01:07:07.560 --> 01:07:13.830
Rommie Amaro: But I will also say that that's that's the other reason why I think it's really important that we have multiple groups developing

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01:07:14.220 --> 01:07:20.760
Rommie Amaro: Models of the spike. So I'm not the only person studying the spike and every, every group that builds the spike protein.

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01:07:21.150 --> 01:07:26.820
Rommie Amaro: They tend to just naturally maybe have made a slightly different choice in terms of the composition

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01:07:27.360 --> 01:07:36.180
Rommie Amaro: Of the of the glycans at a particular site even abiding by what we know from guy comix, you know, there can be varying degrees of micro heterogeneity.

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01:07:37.170 --> 01:07:44.850
Rommie Amaro: And so this is another reason why I come back to I made that comment about the AI at the end because, you know, we're going to have we're assembling as a worldwide community.

397
01:07:45.810 --> 01:07:58.650
Rommie Amaro: A database essentially have a lot of these variations and you know with with new methods analysis method, we should be able to develop a better understanding of, sort of, what are the impacts of the micro heterogeneity on the

398
01:07:58.890 --> 01:08:09.180
Rommie Amaro: structural dynamics and potentially the mechanism and function of these proteins but it's going to take somebody to sort of like, do a meta level analysis, you know, all of these

399
01:08:11.970 --> 01:08:13.290
Rommie Amaro: Yeah, I hope that answered your question.

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01:08:16.890 --> 01:08:26.940
Amy Friedlander: Okay, so the next question is from Ken Chang, how can the current vaccines be quickly modified for the UK and South Africa viruses.

401
01:08:28.020 --> 01:08:35.550
Rommie Amaro: So, um, well, so what they can do is they can modify the spy construct. So, um,

402
01:08:35.970 --> 01:08:46.410
Rommie Amaro: So first of all, the UK strain, I think, has been shown to be like, I think it's fairly okay with the vaccines that there's just like really not too much of a hit to their advocacy.

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01:08:46.860 --> 01:08:56.460
Rommie Amaro: The South Africa strain is a little bit more concerning and even Madonna. Just yesterday, announced that they have an update to the vaccine. So what they can do is just so

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01:08:57.750 --> 01:09:05.460

Rommie Amaro: So, these, these sort of variants of concern or these mutations. It's like the spike protein will you know mutate parts of itself.

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01:09:06.750 --> 01:09:10.200
Rommie Amaro: To do a couple of different things. Generally, it's

406
01:09:11.310 --> 01:09:19.500
Rommie Amaro: Generally, you know, these mutations, they sort of give us some kind of gain of fitness as it's circulating in the case of the South Africa strain bears.

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01:09:19.980 --> 01:09:36.330
Rommie Amaro: Mutation or two mutations in that receptor binding domain that I told you about. And these mutations make that handshake with ace to even stronger. And so that's one of the reasons why it's sort of like it's it has optimized even more sort of this contact

408
01:09:37.350 --> 01:09:47.070
Rommie Amaro: And so what they can do is they can actually change. I believe what they do is they just changed, like the M RNA that they're putting into the vaccine and they can make it so that it's actually mimicking the one that's circulating

409
01:09:48.270 --> 01:09:50.850
Rommie Amaro: But what we need to do is, you know, we hope to do really is.

410
01:09:51.660 --> 01:10:07.470
Rommie Amaro: Get global vaccine, you know, vaccines around the world globally as quickly as possible so that we can, you know, reduce the levels of circulating viruses and keep that mutation down that's going to be like a really big global effort.

411
01:10:09.840 --> 01:10:18.960
Andrew Lovinger: The next question has to do with different open can formers, and how do the simulations capture them. So, single, double, triple open states.

412
01:10:19.260 --> 01:10:30.570
Andrew Lovinger: Does the molecular dynamics work indicate the percent occupancy of those different open states, and is there a preference of different open can formers were engaging the ace.

413
01:10:32.460 --> 01:10:36.210
Rommie Amaro: That's a great question. And there's a lot of us working on it still

414
01:10:38.400 --> 01:10:44.400
Rommie Amaro: We have only seen in all the simulations that we've done, we've only seen

415
01:10:45.540 --> 01:10:55.350

Rommie Amaro: The opening of the one. And we've seen. The other thing is, not only does it open, but that whole they call it the S one sub unit. It actually kind of has to peel off.

416
01:10:57.150 --> 01:11:07.500
Rommie Amaro: And and then it's like there's there there are questions around, you know. So once that guy is up and then once it starts to peel off. Is it easier for the other. So, you know, other Arby's to open

417
01:11:08.580 --> 01:11:13.380
Rommie Amaro: Our work has not revealed that yet although I'm sure that that probably will be coming down the road.

418
01:11:16.380 --> 01:11:23.580
Rommie Amaro: Yeah, you know, and it, it is interesting because you know the spike protein. I mean, one of the parts this like so fascinating, which I really didn't

419
01:11:24.060 --> 01:11:34.020
Rommie Amaro: I really didn't do it justice, but it is a, it really is a spring loaded molecular machine, it is if you look at its structure.

420
01:11:35.010 --> 01:11:39.720
Rommie Amaro: I mean, it's just so amazing how all these pieces come together and

421
01:11:40.530 --> 01:11:50.940
Rommie Amaro: It's right at this margin at this border of being stable and unstable such that you have these relatively small changes and then all of a sudden

422
01:11:51.270 --> 01:12:05.730
Rommie Amaro: Something massive you know there's a really like a massive confrontational change that it goes from like the pre to the post fusion states and sort of, you know, it's just amazing to me how

423
01:12:07.860 --> 01:12:09.570
Rommie Amaro: These microscopic

424
01:12:10.620 --> 01:12:15.330
Rommie Amaro: These microscopic change something as simple as, like, a single amino acid mutation.

425
01:12:16.380 --> 01:12:19.170
Rommie Amaro: Can completely shift the landscape of this protein.

426
01:12:19.770 --> 01:12:29.280
Rommie Amaro: And these are the kinds of things that yes and like the simulation can can inform on but you know we're still seditious little lot to be done. And I'll just, I'll just just underscore that too. I mean, not to get too biological about it but

427
01:12:29.640 --> 01:12:32.550
Rommie Amaro: You know, one of the big discoveries of this protein.

428
01:12:33.600 --> 01:12:38.460
Rommie Amaro: That came years ago was actually the so called to P mutation, you know, which

429
01:12:39.120 --> 01:12:48.000
Rommie Amaro: Maybe some of you have heard about. But this was largely the work of Jason. The Cleveland working on the MERS protein, the sort of sister relative to this source code to

430
01:12:48.720 --> 01:12:58.560
Rommie Amaro: Where you know they were trying to, they were trying to get the protein to express better and so that they could characterize the pre fusion state structurally

431
01:12:59.160 --> 01:13:17.040
Rommie Amaro: And they realized that they could make a to proline mutate they could mutate some residents to proline at the tip of the sort of central Ulysses and that was a complete game changer. The small modification stabilized to a dramatic effect. The, the pre fusion state.

432
01:13:18.330 --> 01:13:27.000
Rommie Amaro: You know, changes the expression makes it much more experimentally tractable to work with, but it also changes the amount of the RB DS that are in the upstate

433
01:13:27.660 --> 01:13:35.340
Rommie Amaro: And this is why the vaccines turned out to be so effective because if you just put in the wild type spike. You have a particular

434
01:13:35.910 --> 01:13:45.420
Rommie Amaro: Like you're saying ensemble up and down states, but when they made that to pee mutation. They think shifted that confirmation to having mostly the one upstate

435
01:13:45.930 --> 01:13:54.900
Rommie Amaro: And that's why, that's why this two piece by construct that's in the Madonna vaccine. It's in the Pfizer vaccine that's in every vaccine, except for esters Annika with the two p

436
01:13:55.410 --> 01:14:06.690
Rommie Amaro: Is it's like they, it was, it was very. It was hot. It was it was much better at getting a response from the human immune system and it was because that one. The tiny mutations basically shifted it to a much more exposed state.

437
01:14:07.590 --> 01:14:15.030
Rommie Amaro: Anyway, so yeah I'm we're trying to with others, you know, really understand what are all these sort of details of the molecular mechanism.

438
01:14:18.780 --> 01:14:28.080
Amy Friedlander: Wonderful, thank you from another attendee, can you discuss the error margins in your simulations computer scientist, I'm sure.

439
01:14:29.130 --> 01:14:37.230
Rommie Amaro: Um, yeah, I mean, so we characterize error in different ways depending sort of on what we look at. So I'm not sure exactly

440
01:14:37.770 --> 01:14:45.060
Rommie Amaro: But, like, one way that we care. You know, we often look at sort of deviation from the main. So a lot of what we're looking at is like statistical

441
01:14:45.540 --> 01:14:59.760
Rommie Amaro: We're looking at sort of like what are the statistics of populations of the upstate or some kind of what's the variance in dynamics in terms of which we always have to sort of define in some way. So maybe it's like I didn't show you this, but there's

442
01:15:01.110 --> 01:15:10.410
Rommie Amaro: There's a when we characterize the dynamics coming out of our system, we're looking for. Sort of like predominant motions. It's not this that you see, like, one thing you see

443
01:15:10.920 --> 01:15:19.200
Rommie Amaro: You see sort of like distributions of motions and and so you characterize in that sense. And that's not air that's more like maybe the results.

444
01:15:21.600 --> 01:15:28.050
Rommie Amaro: So maybe I need to think more carefully about how I can succinctly reply to how we characterize error. But in general, we do it by

445
01:15:30.000 --> 01:15:35.850
Rommie Amaro: Trying to benchmark back to what is known experimentally.

446
01:15:38.040 --> 01:15:38.700
Rommie Amaro: But

447
01:15:40.170 --> 01:15:48.090
Rommie Amaro: Yeah, there's sort of like it comes in quantification of error from molecular simulation comes into play in many different ways from

448
01:15:48.750 --> 01:15:57.300
Rommie Amaro: From the molecular dynamics engine itself, all the way through to development of force fields, which I didn't talk about, but they're like part of the ingredients that we need to run the simulations.

449
01:15:57.630 --> 01:16:03.030
Rommie Amaro: And then also how we sort of like analyze the data. So it comes into play. Actually, in many different ways.

450
01:16:05.010 --> 01:16:17.970
Andrew Lovinger: Okay, thank you. Next question is from yourself. My yep scheme, you would like to know about rigidity of the S protein. So why is it so Richard and always sticking at 90 degrees from the surface member

451
01:16:18.810 --> 01:16:24.960
Andrew Lovinger: One would expect a lot of bending changes in orientation visa v. The surface or the virus surface.

452
01:16:26.220 --> 01:16:34.110
Rommie Amaro: It does. It does. It does move. It's just that the pictures that you see there only showing you one thing.

453
01:16:34.680 --> 01:16:48.300
Rommie Amaro: So this is like you know you like struck new strike to my heart with this question because that's how it is that we see something and then we sort of imprint that that's how it is everywhere. When it's absolutely not so

454
01:16:50.130 --> 01:17:02.100
Rommie Amaro: You see this pretty image of this tidy standing very sort like a little soldier spike protein. It's not at all the case, it bends like crazy, it bends. It has all sorts of angles.

455
01:17:02.850 --> 01:17:07.470
Rommie Amaro: You know, sort of like I showed you with the stock and they know from cryo et if they look at

456
01:17:08.160 --> 01:17:14.820
Rommie Amaro: So the reason why we sort of depict it like straight up and down, it's just because the cryo electron microscope is a single particle

457
01:17:15.240 --> 01:17:24.630
Rommie Amaro: People you know they get the head and then it's like, it's just they just see this every lab. And it's, you know, it's just they oriented in a certain way and then the rest is history.

458
01:17:25.110 --> 01:17:36.180
Rommie Amaro: But if you look at the cryo electron tomography, which gives us like many pictures of the spike on the surface of the virus as soon as you start to assemble those you realize, oh, this guy has major hinges.

459
01:17:36.300 --> 01:17:43.620
Rommie Amaro: And it can, you know, it can it can lean quite far over and that's not only it carries through for every single protein that like we've ever studied since

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01:17:43.980 --> 01:17:48.810
Rommie Amaro: Since like the beginning of time, and it's definitely the case with the viral proteins to just like I showed you for is to

461
01:17:49.200 --> 01:17:54.630
Rommie Amaro: Is to, if you look at that crow electron microscopy study you see it standing very upgraded okay it's ready to go.

462
01:17:54.930 --> 01:18:03.600
Rommie Amaro: But actually it's waving around and it goes almost literally nearly like flat to the membrane. And then it can go back and forth. And these sorts of

463
01:18:04.590 --> 01:18:13.740
Rommie Amaro: Properties as you, you know, suggest. They're important for sort of like the mechanical the mechanics of membrane fusion that it has these different hinge points and that

464
01:18:14.160 --> 01:18:26.910
Rommie Amaro: Allows for binding and contact you have flexibility and bringing those two membranes close to the end for fusion. And so it's all part of it's all part of their mechanism. It's just we're only now getting insights into how these things actually move

465
01:18:30.030 --> 01:18:45.450
Amy Friedlander: So I think we have a related question from Randall Lynch, but I'll pose it just to make sure can. The simulation work on the viral membrane. The model to capture the types of curvature changes that would be important in viral budding or infusion with the host memory.

466
01:18:46.830 --> 01:19:02.370
Rommie Amaro: Yes, we can. It's just, I will say that's a place where course graining has a lot to give like the work of Greg both he's done a lot of good things in that area with like he looking at HIV virus type budding and assembly.

467
01:19:03.420 --> 01:19:16.650
Rommie Amaro: So we can do it. And we can we can get the curvature. So I showed you know I like with influenza. It's like, it's like all these things, they're not actually really spherical. They're sort of like mostly spherical, but they're, you know, they're not. And sometimes it can be filaments and stuff.

468
01:19:19.860 --> 01:19:27.420
Rommie Amaro: It's just that for our methods because we're carrying around all the details of the atoms, which is wonderful for things for questions about mechanism.

469
01:19:28.440 --> 01:19:36.540
Rommie Amaro: For chemistry, you know, if you want to understand how to design new chemical matter that could affect biological function, you need the atoms. Let's face it.

470
01:19:37.350 --> 01:19:49.410

Rommie Amaro: But, you know, if you want to look at more longer scale properties larger link scales longer time skills, then you know methods like course grading, which can link to our structures, but then

471
01:19:49.830 --> 01:19:59.730
Rommie Amaro: They reduce the resolution allow for longer time stepping and bust can sort of get out towards longer timescales of of fusion. And also, you know, a budding

472
01:20:00.150 --> 01:20:06.720
Rommie Amaro: That will come and I think I'm, you know, I'm really one of the also sort of silver linings is, you know,

473
01:20:07.380 --> 01:20:21.060
Rommie Amaro: In general for the type of work that we do. We are, in some sense, we, we are really reliant on on good experimental data to like give us checkpoints, you know, for what we're simulating like sanity checks testing of hypotheses, but

474
01:20:21.360 --> 01:20:31.530
Rommie Amaro: Like with source code to now there's so many good data sets. And I think we're going to, it's going to allow for like an acceleration of methods development and scientific understanding you know it's going to be, you know,

475
01:20:31.980 --> 01:20:36.840
Rommie Amaro: Focus here because this is where the data is. But I'm sort of excited for that.

476
01:20:39.240 --> 01:20:55.830
Andrew Lovinger: Thank you. Next question has to do with vaccine testing. It's from Ken Wang would like to know and molecular simulation contribute to increasing the efficiency of vaccine testing and evaluation, for example, not creating the conditions for testing in the population.

477
01:20:57.840 --> 01:21:00.930
Rommie Amaro: Oh, that's a really good question. That one goes beyond my pay grade.

478
01:21:02.640 --> 01:21:21.030
Rommie Amaro: Um, you know, we're using. We're going to try to use more like a simulation to design like a broadly to to sort of help in efforts to make a broadly neutralizing coronavirus like pan coronavirus vaccine but that's like on the development side in terms of clinical trials.

479
01:21:22.110 --> 01:21:34.380
Rommie Amaro: I would guess that it's going to be mostly about like understanding, maybe the genetics of the populations and making sure that it's like broadly distributed and stuff like that. But I actually I'm

480
01:21:35.760 --> 01:21:39.270
Rommie Amaro: Not one. I should stay in my lane. Sorry.

481

01:21:42.930 --> 01:21:50.580
Rommie Amaro: Which is to say, I'm sure there's probably something they could be done, but it wouldn't be like, necessarily. I don't think with molecular simulation. But I mean, I'm sure computational methods in general.

482
01:21:52.440 --> 01:21:57.810
Amy Friedlander: So the next one is a bit of a comment. But I wondered if you would just take a few minutes to reflect on it.

483
01:21:58.500 --> 01:22:02.910
Amy Friedlander: From Miranda lunch again absolutely beautiful work and talk and it is wonderful.

484
01:22:03.210 --> 01:22:09.630
Amy Friedlander: To hear about the value of and commitment to open data open source code and creating an open computing community.

485
01:22:09.900 --> 01:22:15.870
Amy Friedlander: Rami I know you talked about this in your talk. But do you want to linger a few minutes and just think a little more out loud.

486
01:22:16.260 --> 01:22:27.090
Amy Friedlander: About the importance of Open Science and and the open the open the open communities in which you have engaged and to which you contribute and from which you have benefited

487
01:22:28.710 --> 01:22:35.790
Rommie Amaro: Or. Sure. I mean, because it's one of my favorite things to talk about because it just makes me feel so good. You know, so I want to say.

488
01:22:38.220 --> 01:22:44.610
Rommie Amaro: Yeah, I mean, it's been it's just been sort of like I said, it's been a very special time. I think that it's been

489
01:22:45.120 --> 01:22:50.760
Rommie Amaro: Particularly good so I mean one of the things about this pandemic has been that it has, you know, really.

490
01:22:51.600 --> 01:22:59.940
Rommie Amaro: It's sort of like when you get in these situations it shines lights right so it's like it's shining the light on what we do well it exposed strengths, but it also exposed weaknesses and I think

491
01:23:00.570 --> 01:23:13.140
Rommie Amaro: For science, you know, I'm hoping that in molecular simulation. I'm really hoping that some of these things stick around because, you know, I'll tell you, in general, even after ordinarily even after we get the paper and

492
01:23:13.980 --> 01:23:19.350

Rommie Amaro: We still don't share our methods. We still don't share our system files we don't share trajectories.

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01:23:19.860 --> 01:23:31.110
Rommie Amaro: Um, you know, I think that this is really helping to change that. That's something that in small segments of the community, people have been talking about for years. We need to share these things we need to be open about it.

494
01:23:31.500 --> 01:23:40.890
Rommie Amaro: Because you know for reproducibility for training and for like the future discovery for building on these initial models. It's so important no matter what area of science. It's wrong.

495
01:23:41.190 --> 01:23:47.010
Rommie Amaro: And we've been reluctant to do that and you know it's funny. I don't know for me like there's something I think it's a couple of things like why we haven't shared

496
01:23:47.820 --> 01:24:02.310
Rommie Amaro: One is, actually, to be honest, like so, are weighted ensemble trajectories. They're 200 terabytes. It's not easy to share 200 terabytes of data, like there's, there's, it's like a complication. It's like a bit of a complicated thing. It takes some thought.

497
01:24:03.450 --> 01:24:06.210
Rommie Amaro: Especially if you're just like, if you're a small research group.

498
01:24:07.080 --> 01:24:19.980
Rommie Amaro: You know, how do you really how do you maintain that other people have access to this and the system is not really set up the journals, don't take care of it for you, you know, since like we have to sort of change how we're doing it the creation that the of the

499
01:24:21.600 --> 01:24:32.490
Rommie Amaro: Sort of molecular structure and therapeutics hub that Molesey started, I think, was fantastic, and a really great sort of step in this direction and it catalyze a lot of discussion among us about

500
01:24:33.030 --> 01:24:46.050
Rommie Amaro: What are the, what's the metadata that we need to provide with simulation and, like, how do we if like if like hundreds of groups around the world are actually putting in these data sets. Like, how do we judge. What's good, what's bad or, you know,

501
01:24:47.070 --> 01:24:55.200
Rommie Amaro: A lot of those conversations, which need to happen, which often don't happen because we're so busy talking about other things, you know, they're starting to happen now. And I think that's going to be very good for the field.

502
01:24:55.710 --> 01:25:01.890
Rommie Amaro: So I'm looking forward to that carrying forward. And then, of course, just, you know, the whole

international aspect effort of it, which

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01:25:03.360 --> 01:25:06.030
Rommie Amaro: Has just been fantastic. So I think that

504
01:25:06.660 --> 01:25:10.410
Rommie Amaro: You know, and it's sort of like the move to remote like I've participated. I was

505
01:25:10.530 --> 01:25:20.460
Rommie Amaro: Saying I think before they have given so many seminars and in so many places all around the world that I'd never would have been able to fly like plan to all these places just logistically never could have happened.

506
01:25:20.910 --> 01:25:33.300
Rommie Amaro: But it's like we can have these conversations and I can have, you know, research lab meetings with people in in the UK or in Spain or wherever and you know it's much easier. So hopefully these types of open

507
01:25:34.560 --> 01:25:41.970
Rommie Amaro: You know this. Hopefully that will be one of the good things that sort of sticks around after the pandemic, to some extent.

508
01:25:44.190 --> 01:25:44.850
Andrew Lovinger: Yes, indeed.

509
01:25:45.870 --> 01:25:54.120
Andrew Lovinger: Second question, who can whine. How can genomic and molecular work combined to anticipate than likely space or future mutants.

510
01:25:56.460 --> 01:25:57.780
Rommie Amaro: Yes, um,

511
01:25:59.370 --> 01:26:02.550
Rommie Amaro: Well, I mean there. Hopefully are

512
01:26:03.600 --> 01:26:12.420
Rommie Amaro: You know, I mean, one can imagine being much better at predicting which strains are going to

513
01:26:13.260 --> 01:26:22.980
Rommie Amaro: Be the ones that actually circulate and this is the kind of thing that's important, not just for school to and future mutations. But for things like influenza for like many diseases.

514
01:26:23.490 --> 01:26:34.290
Rommie Amaro: You know, but there's lots of things that we have yet to understand, you know, like for example why

you know all of these pandemic diseases basically come from animal reservoirs at some point.

515
01:26:35.940 --> 01:26:39.870
Rommie Amaro: So understanding that switch that species switching

516
01:26:42.330 --> 01:26:54.150
Rommie Amaro: is also very important. And that's sort of again more basic science but like if we know more about those mechanisms. If we can really begin to understand where are those important tipping points.

517
01:26:55.230 --> 01:27:06.810
Rommie Amaro: Then that hopefully will, you know, with just by genomic surveillance could make a flag like an alert, like, okay, you're getting this is getting sort of seems like it might be getting, you know,

518
01:27:07.770 --> 01:27:17.700
Rommie Amaro: To something that we need to be more concerned about and that could be either for the current disease as it circulating or for, you know, anticipating future pandemics, whatever they may be

519
01:27:22.650 --> 01:27:29.880
Amy Friedlander: So really, you've had a long day. And you get to work even harder when we invite you back to visit with

520
01:27:30.840 --> 01:27:40.410
Amy Friedlander: Our colleagues at the NSF at four o'clock. So although we do still have some questions that will share with you and perhaps you would like to address them when you come back with us at four.

521
01:27:40.830 --> 01:27:50.910
Amy Friedlander: I think we had to give you a break and thank you for all that you've shared with us today and for all that you do every day. So please, every

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01:27:51.930 --> 01:27:52.470
Amy Friedlander: Virtual

523
01:27:55.110 --> 01:27:59.550
Rommie Amaro: That's great. Thank you so much. Well, I lose these questions. I was just thinking I should try to

524
01:28:00.240 --> 01:28:01.440
Amy Friedlander: Know will capture them for you.

525
01:28:01.920 --> 01:28:05.880
Rommie Amaro: Okay, that would be great because I don't know how many screenshots. I can do. Okay, good, good.

526
01:28:06.360 --> 01:28:09.720

Amy Friedlander: No, I'm going to rely on memes to work their magic.

527
01:28:10.380 --> 01:28:13.710
Rommie Amaro: Okay. So hi, Lynn, I'm sorry. Of course you're part of I'm

528
01:28:16.830 --> 01:28:17.340
Lin He: Sorry.

529
01:28:18.540 --> 01:28:19.380
Rommie Amaro: I didn't know that.

530
01:28:20.910 --> 01:28:22.740
Lin He: chemistry questions, waiting for you.

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01:28:23.700 --> 01:28:24.570
Rommie Amaro: Oh, good, good, good.

532
01:28:24.930 --> 01:28:25.290
Lin He: Good.

533
01:28:25.920 --> 01:28:26.700
Good. Wonderful.

534
01:28:27.900 --> 01:28:33.990
Amy Friedlander: Presentation. Thank you. Thank you know and I see you're still on anything you want to say.

535
01:28:34.740 --> 01:28:41.430
Alan Tessier: Oh, just, it was a fascinating talker. I'm very much thank you Amy for for having

536
01:28:42.540 --> 01:28:43.770
Alan Tessier: Given this course.

537
01:28:45.090 --> 01:28:47.460
Amy Friedlander: Thank you for the pleasure. Thank you.

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01:28:47.820 --> 01:28:49.530
Andrew Lovinger: So I will see you at four o'clock to

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01:28:49.620 --> 01:28:55.530
Amy Friedlander: Do it for. And I think Blaine, or Michelle, if you could capture the questions for us.

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01:28:56.580 --> 01:28:57.450
Amy Friedlander: I'd be grateful.

541
01:28:58.860 --> 01:28:59.430
Thank you.

542
01:29:00.570 --> 01:29:00.930
Okay.

543
01:29:02.010 --> 01:29:03.540
Amy Friedlander: Everybody be well be safe.

544
01:29:04.110 --> 01:29:04.410
About