Episode 7 – COVID, chaos, computation: what mathematics can tell us about pandemics

Guest: Alhaji Cherif, PhD

Peter Kotanko
Welcome to the Renal Research Institute's Frontiers in Kidney Medicine and Biology, where we share knowledge and advances in kidney research with the world.

In this episode of Frontiers in Kidney Medicine and Biology, we talk with Dr. Alhaji Cherif, principal mathematician at the Renal Research Institute.

We discuss COVID chaos and computation - what mathematics can tell us about pandemics. Dr. Cherif has trained with some of the world's leading mathematicians, and he is bringing his expertise to projects as diverse as COVID-19, bone metabolism, and anemia management.

It's such a great pleasure to welcome today to Kidney Medicine and Biology Dr. Alhaji Cherif, who is an esteemed mathematician, he is specialized in applied mathematics. So welcome, Alhaji.

Alhaji Cherif
Thank you, Peter. Thank you for having me.

Peter Kotanko
No, my pleasure. So, Alhaji, you are an applied mathematician. Just help me to understand this. I mean, we all have mathematics in school, but there are these applied mathematicians, then the pure mathematicians, and is there another species of mathematicians? What's actually the difference there?

Alhaji Cherif
So applied mathematicians usually deals... tend to deal with real world application. So, we basically write equations to describe the real-world problems, phenomenon, and trying to model them by equation formulas, to better understand them by managing them or predicting them more efficiently.

And pure math, in a sense, deals more with abstractions and deals with the abstract entity, and tries to find the relationship between these different abstract entities.

In a sense, pure math tries to understand deeper mathematics itself, whereas applied math, tries to apply some of those tools in more real-world cases. And you might even be familiar with this.

So, whenever you go to your doctor, and your doctor writes a prescription for you, in a sense, they are using equations to give you the dosing that you need for your prescription. So, in a

sense, by not directly telling you, that is what they are doing. So, that is what applied mathematics is.

Peter Kotanko
Interesting. I try to recall when my doctor… I, would use a calculator the last time when prescribing something to a patient, but you are referring to the background, say pharmacokinetics, pharmacodynamics. They will evaluate this. Which actually brings me to the next question, Alhaji. How can applied mathematics actually help patients? I mean, do you have a few examples where applied math has really made a difference?

Alhaji Cherif
Definitely. So, there are a lot of areas that applied mathematics has been useful. So, like in the medical world like a CT scan, right? It's actually driven by a lot of mathematical models. But, in recent years, mathematical models have been used where we use it to evaluate the effectiveness of new drugs, or a new procedure. We use it to, like say, in the cancer world, you look at it, they use it to estimate the survival rate of cancer patients undergoing a certain type of condition like glioblastoma. For example, mathematics has always been used there in conjunction with computational tools to understand the growth of cancer, and how to control them for more than two decades. Right?

So, here mathematics allows you to understand the challenges in cancer treatment, including drug resistance, and relapses. And, in my own work, we use mathematical models in renal anemia, where mathematics is used to provide administration dosing to patient or mathematics can also use to understand some of the pathophysiological processes that may not be fully understood but allow us to understand some of the intricate diseases of these particular fundamental processes. So, mathematics can actually use... applied mathematics in this context, can be used a lot in helping patients improve their health outcome and have better treatment protocols.

Peter Kotanko
This is actually really interesting. When you think about it, say you have an imaging done, you get drugs prescribed, that, on so many levels, mathematics is really involved. It's like, don't know, using a smartphone. And you don't realize how much math is actually embedded there and nothing would work without mathematics. So...

Alhaji Cherif
Exactly, even if you do like a Google search, right? Google searches have a page ranking, so that's the mathematical underlining. Or, if you get recommendations on YouTube or other sites, like when you're shopping. All of these are mathematical underpinnings, and they might come with different names. Some people might call it machine learning. Some people... and sometimes it's just a mathematical model based on data, analyzing the data that you are generating.

Peter Kotanko
I mean, these days, in the midst of 2021, it is very difficult to talk about anything without talking about COVID-19. And I know that you are conducting active research into some aspects of COVID-19, and how to describe those aspects mathematically. Can you give us a few examples? I think you published about pool testing, you published about the reproduction number, and other work. So, can you just give us a few examples, and tell us how you approach those?

Alhaji Cherif
I work on several mathematical models related to COVID. So, one of the projects that I am working on is analyzing actual COVID cases, among our patients, using within a host immunological model to understand how our patient responds to infection, or even to vaccination. And this can be used to predict which patients are more likely to need additional vaccination or how soon they will need additional vaccination.

The other project that I've worked on... you mentioned them… pool testing. So, here, we try to find a way how to better test patients with using less resources. So, and then, also reproduction number in this case, this is a component where we try to look at the incidence data and try to understand how well we are controlling COVID in our patients, compared to the general population, and how we are doing in terms of policies that are embedded in controlling this disease.

Peter Kotanko
Now, let me come to pool testing. Actually, I believe some of the members of our audience may want to Google pool testing, and actually, when you do it, I did it a few weeks ago, it's mainly about testing swimming pools, you know. So, what actually is pool testing in the context of COVID-19?

Alhaji Cherif
So, what pool testing is, is a way to actually gather a bunch of samples and test them, in a single shot. So, imagine that you have 10 patients. Now, one way you can do it traditionally, is to test every single patient. So, in this case, you will do 10 patients. Pool testing is saying, basically, depending on some of the characteristics of the disease, and the testing device you're using, you can just lump all those 10 patients into one sample, and then test that. So, in this case, you can see if the patients are negative, you only perform a single test there, instead of doing 10 tests, in order to find out that all those 10 individuals are negative. But however, if the patient that you lump in those groups, one of them are negative, I mean are positive, right? Then, you test every individual one, but if they're negative, you only have performance in good tests. So, pool testing allows you to kind of reduce the number of tests that you perform, speed up the testing procedure, and then without basically spending too many resources on doing surveillance.

Peter Kotanko
Okay, no, no, this is actually a good explanation. But now, let me think this through a bit. So, you said, "well, you have samples from 10 patients, you put them together, and then you test. If the

test for this pool of this group is negative, then you can say, very likely, none of those 10 subjects has COVID-19." But, I mean, say you're living in other circumstances where a larger number of patients have COVID-19. So, what I think it is called prevalence in the term of epidemiology. Say you have a prevalence of 20%? So, that one in five is positive on average. I mean, how would that work then?

Alhaji Cherif
So, what we did in our paper, is to look at in what conditions the pool test is more beneficial. So, we show that, generally, if you're above 30%, pool testing is less effective, it's actually useless in that context. But if you're below 30, in some sense, you can actually test it. So, but the higher your prevalence increases, the more likely that you will miss some of those patients. So, the recommendation is that a pool test, in general, is better when you have a lower prevalence, let's say 1% or 2%, like in a single digit, then it's more efficient to use pool testing. But, as you increase the prevalence, then you start... even it can still be, can provide cost savings to you, but you risk missing some of the patients that you were supposed to detect. „ Which due to the dilution effect, you increase the negative and the number of negative, false negative in the parlance of epidemiology.

Peter Kotanko
Okay, so I think this makes a lot of sense. Say, if it's only one, and I'm making up an example, if only one in 50 patients has COVID. And you pool... and you have 50 patients, (then?) you want to test and group them in, in five pools with 10 samples each, then there might only be one pool, positive, and then you just have to test all these 10 specimens in that pool separately. But for the other 40 patients, actually four tests1 are enough, right?

Alhaji Cherif
Exactly.

Peter Kotanko
Yeah. Okay. Now, this is actually a really smart method, is this method around for a while, or did it just come up with COVID-19?

Alhaji Cherif
So, actually, the method has been around more than 30 years. So, they have used them in blood, like a blood bank, where they are used in order to minimize the sample test, because in this case, the prevalence of some infection in your blood, in this blood bank is much lower, so it's more efficient there. They have used them in HIV testing in the early age of HIV. And I've also used them in some other, STD, infectious disease, but now it's become more discussed during COVID. Because of, you know, historically, we were behind on testing availability. So, in a sense, pool testing has a re-emergence of concept, or even a few years ago was kind of thin.

Peter Kotanko
That's, that's interesting. I mean, is pool testing actually done somewhere? Is it, say, FDA approved? What's the status there?

Alhaji Cherif
A few months ago, around the same time, we had a paper, FDA actually had recommendations on pool testing. And that recommendation was done to more than 5. Right? And that makes sense, because the prevalence in some areas were much higher than what we recommended that you should do to pool test. So, it's used, for COVID, in a sense, there was a recommendation regarding pool testing. But it usually depends on the laboratory that are testing it, and how well]they are able to handle some of the drawbacks, particularly the dilution effect that will eventually emerge as you pool more people together.

Peter Kotanko
Okay, understood. Now, you also conduct other research in the in the COVID world. You're dealing with estimating reproduction numbers. Can you just remind me, and maybe also some in the audience, of what actually is the reproduction number? What is it used for? What kind of research are you conducting on the reproduction number?

Alhaji Cherif
The reproduction number is actually a measure that public health officials use in order to see whether or not one disease is more likely to spread out quickly, or it can be suppressed? Right? And generally, when it's above one, it's considered that the disease has a higher likelihood of spreading through the population and be maintained in the population. When it's less than one, it means it can be suppressed easily.

But what it actually means is that the expected number of an individual person, infected person, can spread the disease to another. So, for example, let's say if I'm infected, right? And if I infect two people. I'll have a reproduction number of two, because during the course of my disease, I'm able to spread the disease to two people.

And if each of those individuals spread the disease to two other people, and so on, then eventually what you will see on average, we will still have the reproduction number of two. Now, or I can easily see that if I infect one person, and each of those individuals infects one person, with some probability, that one of those patients will not infect anyone, and then the disease can disappear. Right? So, it will stop once all your previously infected, recovered. So that's what it measures.

Peter Kotanko
And say, for example, if a production number of, 0.5, would it actually mean that two people on average would infect only one? Is this correct?

Alhaji Cherif
So, because it's a game of average, right? So, it means that, in fact, if you average those two people, so it's possible that one, person infected one person, right? But the other person did not infect anyone. So, therefore, they have an average of 0.5. So, yeah.

Peter Kotanko
Okay, no this is very helpful. And what were the results of your research into the reproduction number in dialysis patients?

Alhaji Cherif
So, what we found is that, if you look at you, if you compare the dialysis population with the general population, the reproduction number overall, were much lower in dialysis population than general population. Of course, there are some sporadic points in time when this is flipped, but overall, the dialysis population were able to better control the reproduction number, even though you also see that the trends, the shape of the reproduction number follows each other. They're similar, almost identical, but the scale, the level of them is actually different.

Peter Kotanko
Why do you think this is the case that the reproduction among dialysis patients would be lower compared to the general population? I mean, I'm thinking like, is it ,could it be that dialysis patients are less outdoors? Because they are, their mobilities average less, or that they wear more masks, or?

Alhaji Cherif
So, it's a combination of factors. So, one possibility is what you actually put your finger on is that dialysis patient are less mobile, right? They move around less around the town, so they're less likely to be exposed to the disease. And, second, they'll test frequently, right?

If you test frequently, you can put in place certain requirements, right? That actually minimizes the reproduction number. So, for example, dialysis patients in clinics are required to wear masks all the time, so that actually minimizes the spread of the disease within the clinic. But also, if that becomes a habitual practice among them, they also are less exposed to being infected. So those are the two, one or two factors that can explain why the reproduction number in dialysis populations will be much lower, but I think the culprit is mostly the lifestyle.

Peter Kotanko
Very interesting. Now, let's change gears a little bit. I mean, you do, of course, a lot of work in COVID. But there are also other projects where you would use mathematical models. Can you say a few words about those projects?

Alhaji Cherif
So, one of the projects that I'm actually excited about is the vascular classification. And this project is pathophysiological, it's a really complicated process. So, we use mathematical models, many data driven approaches, trying to understand the physiology of vascular classification, and at the patient level, trying to understand the drivers of vascular classification with each patient. So, in this case, we use a combination of mathematical modeling, understanding of physiology and also data driven approaches, like in machine learning.

The other project that I am working on is detection of intermittency in oximetry data. So, like oximetry data measures the level of oxygen in your blood, so we try to look at it and to see what kind of pathologies are associated with intermittency. So, it can be intermittent hypoxemia, it can be outside the renal world, fetal hypoxia can generate itself as intermittency. Basically, this allows us to use mathematical models from a dynamical system to try to understand these behaviors in that data set.

Peter Kotanko
This is very interesting. You're looking into oxygen saturation, in the arterial blood, and in signals, and trying to delineate the underlying pathology. That's right?

Alhaji Cherif
Yes. So, because some patients may have a different pathology, and that can actually be seen in data, example, let's say, they have hypoxemia, then the oxygen saturation can be below 90, but that doesn't necessarily mean they should show that intermittency in the data set. But some patients would show intermittency or some patients even though they have oxygen saturation that's above 90, they can still show this intermittency. So, this allows us to actually detect those patterns in the data set retrospectively or in real time by just following some of these signals in the data set.

Peter Kotanko
So, you also work on acid base metabolism, and bone and so, I don't know if you... there may not be enough time to go into any details here, but I find so impressive that you, as an applied mathematician, I mean, you work on different projects from COVID pool testing to acid base metabolism to oxygen pattern to bone metabolism and so on. So, this is quite remarkable. And I think in what I read in your CV in the past you would work on nanotechnology, on questions that came up in that area of biochemistry.

Alhaji Cherif
I was fortunate enough to be exposed to different fields from undergraduate because my original training was actually in engineering. And I was trained in electrical engineering, but then I worked in nano biotechnology, particularly mostly on developing biosensors to detect environmental pathogens in the environment. So, and we also develop mathematical methods to kind of differentiate which design that you need to incorporate, in order to have the most effective configuration in terms of this biosensor's device. And I worked in optofluidic. So, this is using light to move fluid around and at the same time doing PCR within the droplet. So, I was fortunate to be exposed to these different backgrounds.

Peter Kotanko
Do you think that there are actually problems in... specifically in medicine or biology that will most likely remain intractable to mathematics? Or do you think that mathematics in principle has all the tools that would help us to understand this? I mean, one of the reasons why I'm asking is, and I'm a total lay person here, I read that certain mathematical developments were absolutely necessary to move forward in quantum physics. And I'm wondering if, are there

certain mathematically new methods possibly, even necessary, to move into certain areas of this highly complex field of mathematics? Of biology? I mean, and yeah, so what are your thoughts on that?

Alhaji Cherif
I would say, definitely. So, I'm a believer that actually only imagination can limit the ability to solve certain problems. So, I don't necessarily, I wouldn't say it's necessarily intractable for mathematics, just like in hands of who these tools are in and the problem they are interested in either of the availability of the data set, right? Or if we understand some basic understanding of the biology or if we can measure certain quantity. Once we can measure some quantity, I think that is the limitation. So, for example, if you look at topology, right? Topology was completely in the last two decades.

Peter Kotanko
Do you want to say a few words of what topology actually is?

Alhaji Cherif
So topology is basically analysis of sets where the major shapes and structures, right? So, it's in a sense a topological structure of properties. Twenty years ago, it was purely in the realms of pure mathematics. But now, it's actually being used a lot in data science, where you're trying to understand the shape of the data. And it's being used to detect fraud in financial systems, it's used to detect or differentiate different types of diabetes in patients. It's used to treat, to basically different forms of cancers, or shape of cancers. So, which initially was previously unknown, but in the hands of the right person with the availability of computational power, and some other understanding of the system, mathematics can actually help transition to be used in the field that was never taught to be used in before. So, I think, because I'm a little bit optimistic in the use of mathematics, I wouldn't say there aren't any fields that will be intractable, it's just a matter of how the type of data we have and the tools and the skill set of the modeler, how they implement them.

Peter Kotanko
Now, this is actually something really interesting. You said that topology, which was originally just in the realm of pure mathematics, moved over to applied mathematics, is now used in data science. I mean, on the other hand, there is the possibility that certain problems are looked at, like I think about, you know, when the German, mathematician, very famous one, Gauss was working on measurements, and because there was a problem in the real world, this gave rise to new fields of pure mathematics, or do you think it's more of a two-way street? Or do you think that it's primarily pure mathematics that then inspires applications in the real world? Or is it real world questions that are then, lead to developments in, even with pure mathematics?

Alhaji Cherif
So, it can go both ways. I'm a little bit biased toward, because my training is applied math, even though I use some pure math in my work. So, I'm biased in that sense, but generally, it goes both ways. Sometimes some problems actually motivated, like pure mathematical problems, are

motivated by applied questions. And then the pure mathematicians can then go and say, Okay, what is the relationship between this structure right now, it goes into the realms of purely abstract entity.

Now, it can also go the other way around, where the problem started as a pure entity. So, you can see this in the contribution of Hardy, right? So, this is a renowned German mathematician who believed that he would never see his work applied in the real world, so for instance, even pride himself of his contribution, never hurting or helping humanity, right? However, a few years later, actually some of his contributions started to appear in genetics. So, to the point that they even have a principle named after him, like the Hardy Weinberg principle, where they try to look at the distribution of this interaction between recessive and dominant traits, so it can go both ways sometimes.

Peter Kotanko
That's interesting. I mean, and I recall, you know, when, whatever, 30 years ago, when suddenly chaos theory was in, everybody will talk about chaos theory. And it was just, it was, it was something that was, or maybe still is very difficult to understand. Is there actually applications of chaos theory in medicine or biology?

Alhaji Cherif
Definitely. So, but first, I'll just describe what chaos means, right? Chaos is any dynamical system that looks random or irregular. But underneath it, it has very well-behaved deterministic laws that govern this transition. But, it's more sensitive to initial condition. So, if you look at it from that perspective, if you're, let's say, example, the father of chaos used to say, the , my current present, predict my future, right? But my approximate, my approximate present does not predict my approximate future, right? So, in essence, what this means is that if I start with two different initial conditions that are very close to each other, then over time, if you run them, they will actually diverge from each other. So, they'll have completely different features even though they almost started at the same point. In medicine... So, initially in the in the early years of chaos, what you were talking about that people started to try to understand how to apply the concept, right? However, I guess there was more burst in the early phase of the application of chaos, but you can actually look at it without calling it chaos. We do use the technique in our systems. Example, I talked about intermittency, right? How to detect these abnormalities in oximetry data set, right? Where some signals, it seems that they're random, but they're not in theory random phenomena, they actually have certain property certain structure. So, in that particular case, we are in fact using concept for chaos theory to actually try to detect them even though we don't necessarily call them chaotic tools, but there are chaotic tools, either you use recurrence method, or we use entropy to try to detect them. Other ways we can use the concept of chaos, but without really using the term chaos.

Peter Kotanko
Could it be that a random event results in this very small difference in the initial condition and then actually gives rise to chaos as you described it?

Alhaji Cherif
Yes. So, if a system is chaotic, you can even like measurement, error, an example, if the tools you use can probably slightly perturb it, the initial conditions in terms of precision are identical, can actually result in trajectory move apart from each other at certain time in point.

Peter Kotanko
Now, really, thank you, I mean, oh, my God, I could continue with this conversation for hours. I find it just so fascinating to see what can be done with mathematics. Mathematics is so much more than what, I guess, many of us have learned in school, and it actually can be applied to the betterment of patients and to people. So, I really thank you so much. Really, Alhaji, Dr. Cherif, for this conversation. It was a tremendous pleasure having you here, and I'm looking forward, of course, to many more conversations outside of this broadcast. Thank you.

Alhaji Cherif
Thank you. Thank you for having me. Peter.

Peter Kotanko
Thank you for joining the Renal Research Institute for this episode of Frontiers in Kidney Medicine and Biology. We invite you to engage with us on our social media channels and look forward to seeing you again soon for the next episode of Frontiers in Kidney Medicine and Biology.

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