Published: June 2016

Reflections on my time at SACEMA, so far

Alex Welte - Director of SACEMA.

Having been involved in SACEMA since the start, and as director since 2010, Alex Welte is stepping aside to focus on research at the end of June 2016.

It was 2004 when I first met Ekkehard Kopp, an expat South African with a successful career in mathematics and research administration. He was making the case, and sounding out support, for there to be some sort of national research centre for people who were interested in combining mathematical modelling with epidemiology.

I immediately knew that this was a great idea. There I was, trying to do some research along precisely these lines, while based in a department largely focused on classical mathematical applications such as fluid flows and the pricing of complex financial instruments. My attempts to nurture collaborations with clinicians, social surveyors and laboratory scientists were bearing meagre fruit. I had exactly *no* training in biology, demography, epidemiology or statistics; just the physicists standard conviction that mathematics can usefully describe many things, if one follows ones nose doggedly. I was learning about the divides between people trained in medical schools, in laboratories, in statistics departments, as software developers, and as public health specialists; and me, a dyed-in-the-cloth physicist – alone in the corner.

A plot had been hatched, and a start-up grant awarded to Fritz Hahne, a long serving Stellenbosch physicist, with two further South African expats (Brian Williams and Wayne Getz) rounding out the inner circle. A pitch was to be crafted, to a receptive Department of Science and Technology, for some sort of innovative inter-disciplinary entity that would, by definition, apply mathematics to modelling processes like disease spread. The goal would be to shed light on critical aspects of such high level crises as the unfolding HIV and TB epidemics, on which front it was then a particular dark time.

Ekkehard then devoted much of his last sabbatical to a period of road-show and proposal development, which successfully loosed the purse strings of the National Research Foundation; and thus was SACEMA officially born in March of 2006.

That SACEMA has flourished is due to many people. We have been well funded for ten years, with dozens of supportive collaborators around the world. Studies have been designed, data has been cleaned and analysed, and papers and reports have been written, and have found readers. We have punched above our weight in some respects, and many students have thrived here.

It had been a gamble, and we like to think it paid off. Usually, a Centre of Excellence (COE) grant is some kind of reward for a team that has actually demonstrated excellence (the E in COE) for some time. SACEMA was created by its COE grant, on the bet that the time was right for excellence to emerge from inspiration, support, and the palpably present mother of invention. The ice has, thankfully, thickened under SACEMA's claim not to be a centre of mediocrity.

It seems fair to ask whether any lessons can be drawn from our relative success? How is it that with little conventionally appropriate training, our motley crew has made useful contributions to thinking about critical 'policy choices' on the matters of HIV and TB control, and has also developed sensible improvements to methods for monitoring major epidemics such as HIV - where there are consequences to being wobbly in ones explanation of estimates, especially claims about trends.

It would be naïve and self-aggrandising to underplay the tremendous role played by stable core funding, or the gravitas gained by being set up as a national COE, with open doors to government and other major stakeholders. But of course context is not everything – someone still actually has to produce analysis and write it up coherently, and we have not been short of team effort, friends and helping hands.

So there seems to be a lesson here: If one gets a break, and a leg up, and an early, barely earned, pat on the back, then it's worth asking fundamental questions, and it's possible to chart a middle way, where there is room to breathe and find some 'flow', between the various poles to which research is often pulled by funders, fashions, and deadlines. Alas, many researchers never get that break, to turn their ideas into collaborations, outputs, and impacts. It's been a great privilege to be part of this precious space, and I don't plan to abandon it just yet merely because I am handing over the proverbial keys to the big office.

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Focus of my work at SACEMA

My own work, both before and since taking over from founding Director John Hargrove, has largely been on the specific problem of estimating HIV **incidence** i.e. the *rate at which new infections are occurring*, in some population, during some period. Incidence is considerably harder to estimate than **prevalence**, which is simply a *proportion of some population*, at *some point in*, or *narrow interval of*, time, which has some condition (not necessarily adverse – think prevalence of left handedness). Incidence is also much more informative about: i) the recent past, ii) any ongoing unfolding epidemiological 'natural history', and iii) the impact of 'interventions'. John too has been part of this research effort, even while doing the impossible of creating an organisation out of nothing in the early days.

In 'cohorts' (people specifically being followed up in a study), it is simple enough to estimate disease rates by repeatedly testing the same subjects. In open populations, if considering *transient* (of short duration) conditions like seasonal flu, there is not really much difference between incidence and prevalence: The people who currently have flu, are, more or less, the people who became ill with flu within the last week. Slightly more precisely, *the number of people who currently have flu*, is an excellent estimate of *the number of people who became ill with flu within the last week* (even if they are not exactly the same individuals – thus explicitly allowing for variability of disease duration around some average).

The hard part is estimating incidence of *chronic* (long enduring) conditions, in open populations. In this scenario, prevalence summarises, in a complex way, the entire history of an epidemic. It is very difficult to estimate incidence, much less incidence *trends*, from prevalence trends, unless one has really good data on the movement of people, and their mortality – i.e. the other rates at which they come and go.

Many specific lessons about incidence estimation have been learned in recent years, and it's been exciting to see the SACEMA team contribution, which continues to be very active and multi-faceted. We now know that it really is possible to learn something useful about incidence, and even incidence *differences* and *trends*, if one can consistently detect, even in unlinked surveys, sensibly defined cases of 'recent infections' - this in addition to being able to consistently detect plain 'infection'. Following another tack, if one is to 'back out' an incidence estimate from i) prevalence, ii) its rates of change, and iii) the other primary in- and out- flows of people, then, we have learned, there are robust data smoothing methods one can use, in conjunction with solid fundamental mathematical expressions of 'dynamical rules'. Moreover, the requirements on the various inputs to these analyses, if they are to yield useful estimates, can be systematically evaluated in the context of intended 'use cases'.

I've also had the privilege of being allowed to feel useful on projects being driven by others, notably on teasing out the benefits of making early antiretroviral treatment available for all people living with HIV, without waiting for the infection to run the immune system down 'far enough'. The mind set of rationing, adopted by WHO in about 2000, when treatment was very expensive, unproven even in the medium term, and bedevilled by poor reputation in terms of tolerability, proved difficult to shake off. Today, though, it is normal in many contexts to advise HIV positive individuals to start antiretroviral therapy as soon as possible upon diagnosis.

It took some years to assemble to conventional 'evidence' that treatment is a net benefit for patients at pretty much all stages of, not just 'advanced', disease, though this has long been on the spectrum between biologically plausible and likely. Critically, it's been pretty clear for many years, though very hard to digest into policy, that good treatment renders people very dramatically less infectious, so that treatment has actually long been the best 'prevention' intervention available – making a conventional framing of treatment *vs* prevention a dangerous false dichotomy in this case.

This Treatment *as* Prevention (TasP) debate was a stunning example of how mathematical models ultimately don't need to be complex or mysterious, but can provide the means to formally manipulate what we clearly know (known knowns?), into other points which we, by implication, ought to know (unknown knowns?). And perhaps here then is another lesson implied by SACEMA's success in becoming relevant (dare we say 'excellent'?): if you stick to basics, but work through what you know, thoroughly – you can often shed as much light, or more, than if you try to make things very complicated, usually flatteringly framed as 'sophisticated'.

Looking forward

Well, it turns out that the incidence of leadership-turnover at SACEMA is thus far almost precisely 2 per decade, and so, while my research road winds on and on as far as I can see, my role as a unit head

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is turning into the parking lot. The time has come to get fresh legs, fresh blood, and fresh ideas into the director's chair while I wrestle with the backlog on my research to-do list. In a continuation of SACEMA's charmed existence, we have once again hit the jackpot: Juliet Pulliam is taking over as director in July. Coming to us from the Emerging Pathogens Institute in Gainesville, Juliet is a long-time collaborator, most particularly by leading our flagship trans-Atlantic training, mentoring and student exchange visit programme. Perhaps SACEMA will become more responsive in debates on rapidly unfolding scenarios like Ebola and Zika, perhaps the training offerings will jump to the next level, or perhaps we will just have to wait and see exactly how Juliet's energy and vision merge into and swell the collective SACEMA mind stream. I have no worries.

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