Population Modelling by Examples II

by the Population Modelling Working Group

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Introduction

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- The working group maintains a web portal and a mailing list.

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> *“Tackling real-life problems that are relevant at the population level using a range of mathematical tools”*

- However, this is imprecise, so we demonstrate by way of examples.

Robert Smith? (University of Ottawa, Canada)

Polio eradication with synchronised impulses

$$\frac{dS_i}{dt} = (1-p_i)b_i - \mu_i S_i - S_i \sum_j \beta_{ij}(t) I_j - S_i \sum_j \epsilon_{ij}(t) G_j + \sum_j m_{ij} S_j \qquad t \neq t_{i,n}$$

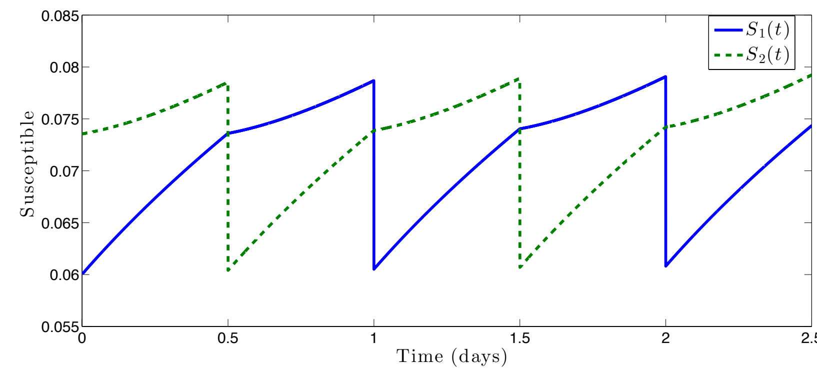
$$\frac{dI_i}{dt} = S_i \sum_j \beta_{ij}(t) I_j + S_i \sum_j \epsilon_{ij}(t) G_j - (\mu_i + \gamma_i) I_i + \sum_j k_{ij} I_j \qquad t \neq t_{i,n}$$

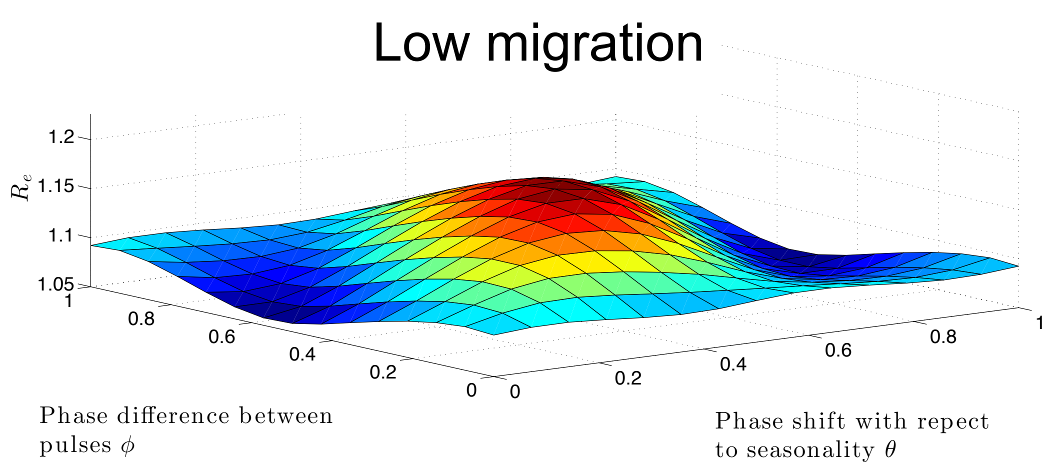
$$\frac{dG_i}{dt} = \xi_i(t) I_i - \nu_i(t) G_i \qquad t \neq t_{i,n}$$

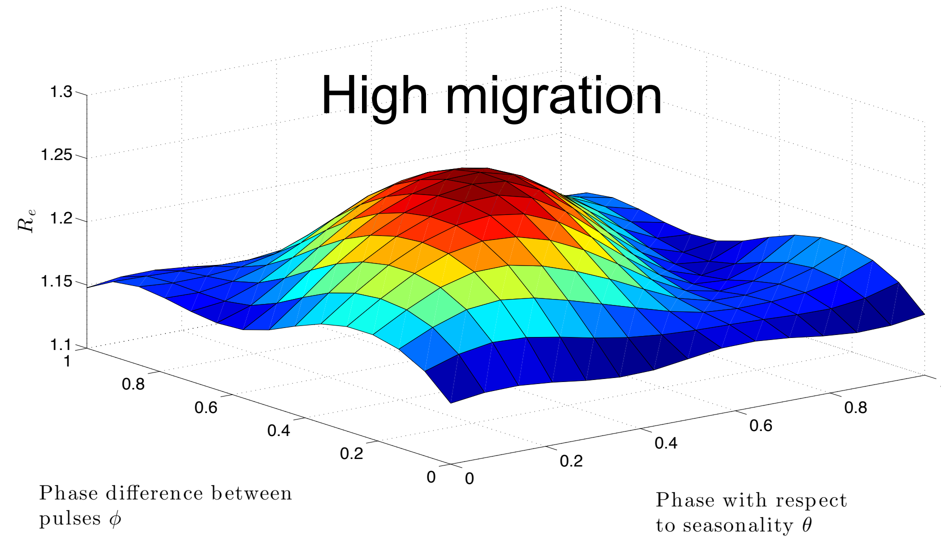
$$\frac{dR_i}{dt} = p_i b_i + \gamma_i I_i - \mu_i R_i + \sum_j l_{ij} R_j \qquad t \neq t_{i,n}$$

$$S_i\left(t_{i,n}^+\right) = \left(1 - \psi_{i,n}\right) S_i\left(t_{i,n}^-\right) \qquad t = t_{i,n}$$

$$R_i\left(t_{i,n}^+\right) = \psi_{i,n} S_i\left(t_{i,n}^-\right) + R_i\left(t_{i,n}^-\right) \qquad t = t_{i,n}.$$

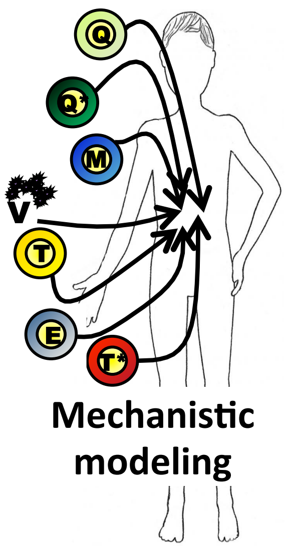




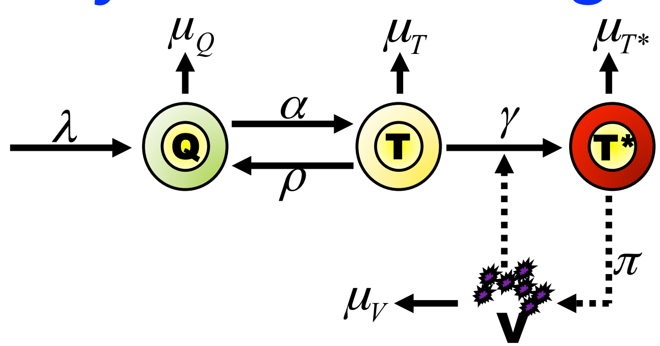


Melanie Prague (Harvard, USA)

Mechanistic modelling of cell population dynamics: targeting HIV drug doses



Mechanistic modeling



Mathematical model (ODE)

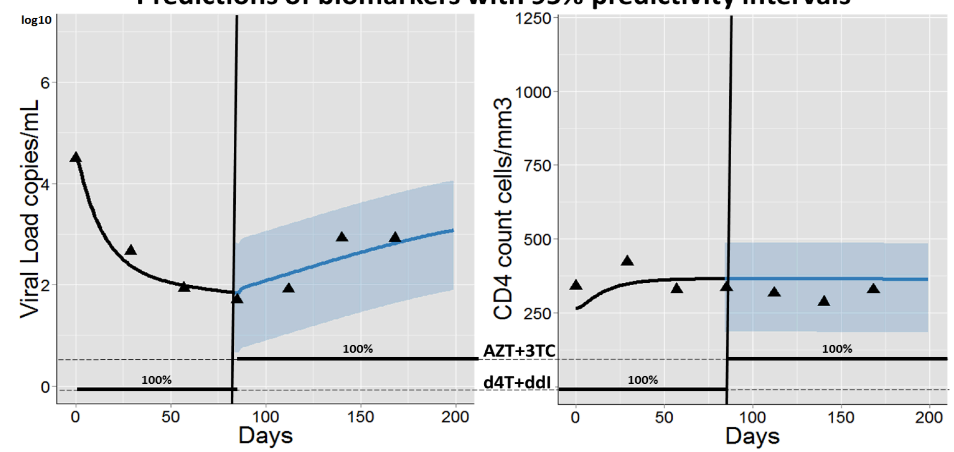
$$\begin{cases} dQ/dt = \lambda^i - \mu_Q Q - \alpha Q + \rho T \\ dT/dt = \alpha Q - \rho T - \mu_T T - \gamma^i(t,TRT)VT \\ dT^*/dt = \gamma(t,TRT)VT - \mu^i_{T*}T^* \\ dV/dt = \pi T^* - \mu_V V \end{cases}$$

Statistical model (NLME)

$$\tilde{\gamma}^i(t,TRT) = \tilde{\gamma}_0 + \beta TRT^i(t) + u^i_\gamma$$
$$u^i_\gamma \sim N(0,\sigma_\gamma)$$

- **Good predictive abilities**

Predictions of biomarkers with 95% predictivity intervals



- **Base reproduction Number (R_0)** characterizes equilibrium leading to infection control and, thus **optimal individual dose (d^i_{opt})**.

$$P(R^i_0(d^i_{opt},\lambda^i,\alpha^i,\ldots,\gamma^i) < 1) = 90\%$$

Matthias Chung (Virginia Tech, USA)

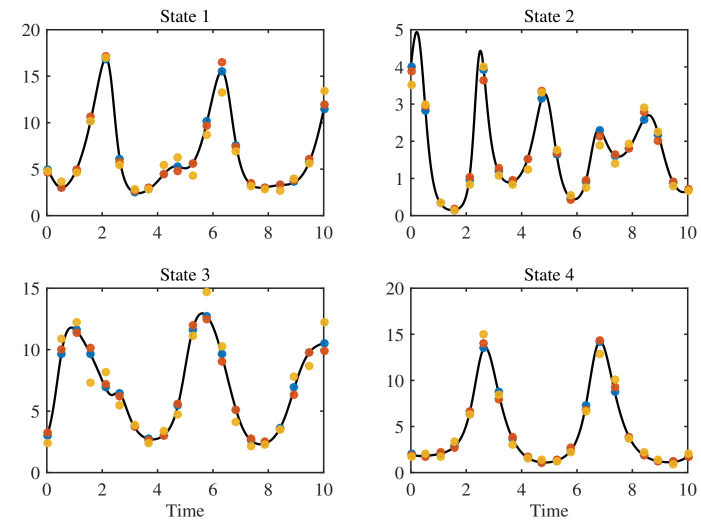
Parameter Estimation for Population Dynamics

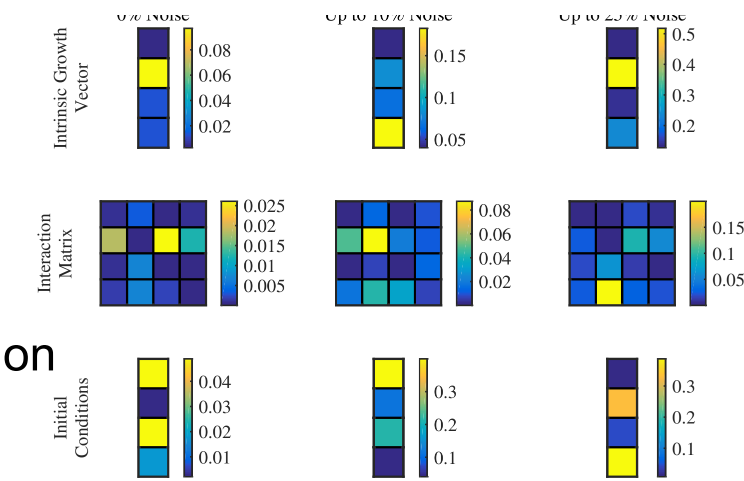
Parameter estimation for *generalized Lotka-Volterra* system

$$\min_{\mathbf{r},\mathbf{A}} \ \|\mathbf{m}(\mathbf{y}) - \mathbf{d}\| \quad \text{subject to} \quad \mathbf{y}' = \operatorname{diag}(\mathbf{y})(\mathbf{r} + \mathbf{A}\mathbf{y})$$

$\mathbf{d}$	observation of species
$\mathbf{y}$	abundance of species
$\mathbf{m}$	projection operator

	distance measure
$\mathbf{r}$	intrinsic growth
$\mathbf{A}$	interaction matrix





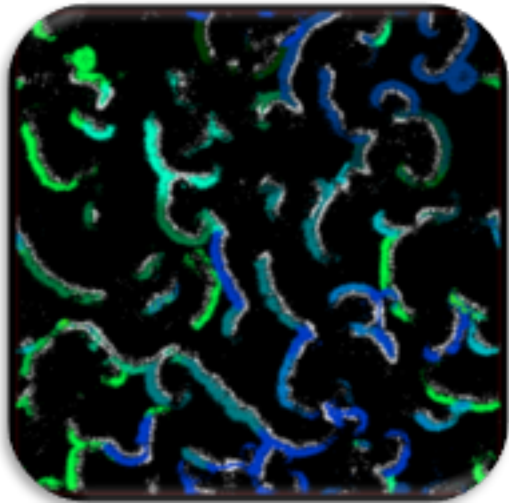
Challenges:

- Complex population dynamics need to be captured leading to investigation of chaotic dynamical system
- Non uniqueness and ill-posedness of parameter estimation problem
- Numerical optimization difficult through non-existence of solution of the dynamical systems

Robin Gras (University of Windsor, Canada)

EcoSim: An artificial world for exploring ecological questions

- Very large populations of "intelligent", evolving agents
- Three trophic levels: grass, prey, predators
- Genome coding for behaviour and physical properties
- Thousands of generations in a few weeks
  - Speciation and species extinction
  - Predator effects on prey behaviour and evolution
  - Sexual/asexual reproduction
  - Invasive species
  - Emergence of communication
  - Emergence of altruism
  - Ecotoxicology.



Valery Forbes (University of Minnesota, USA)

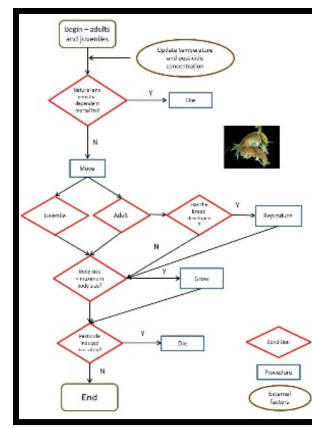
Linking effects of toxic chemicals from the organismal to population level

- Ecological protection goals usually involve populations, not individuals
- We measure effects of toxic chemicals on individual survival, growth and reproduction
- These have variable consequences for population dynamics
- Population models can extrapolate what we need to measure and what we need to protect.

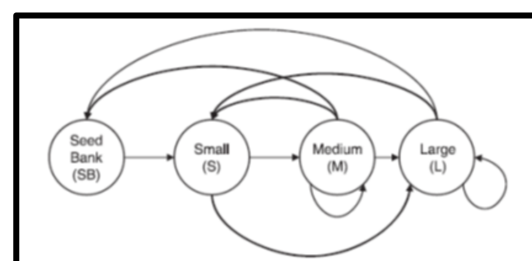
$$\frac{dA}{dt} = \mu NA - \frac{a_{AX}AX}{1 + a_{AX}h_{AX}A + a_{DX}h_{DX}D} - d_A A - e_A A$$

$$\frac{dN}{dt} = I_N + \frac{(1-\delta_{AX})a_{AX}\gamma_{AX}AX}{1 + a_{AX}h_{AX}A + a_{DX}h_{DX}D} + \frac{(1-\delta_{DX})\gamma_{DX}a_{DX}DX}{1 + a_{AX}h_{AX}A + a_{DX}h_{DX}D} + mD - \mu NA - e_N N$$

Scalar Model



IBM

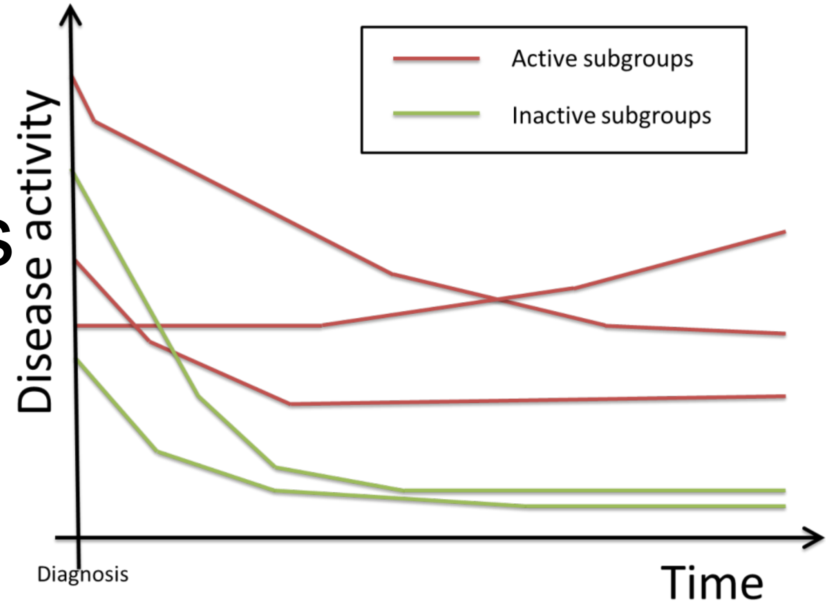


Matrix Model

Sixten Borg (Lund University, Sweden)

Heterogeneity in disease activity and cost-effectiveness analysis

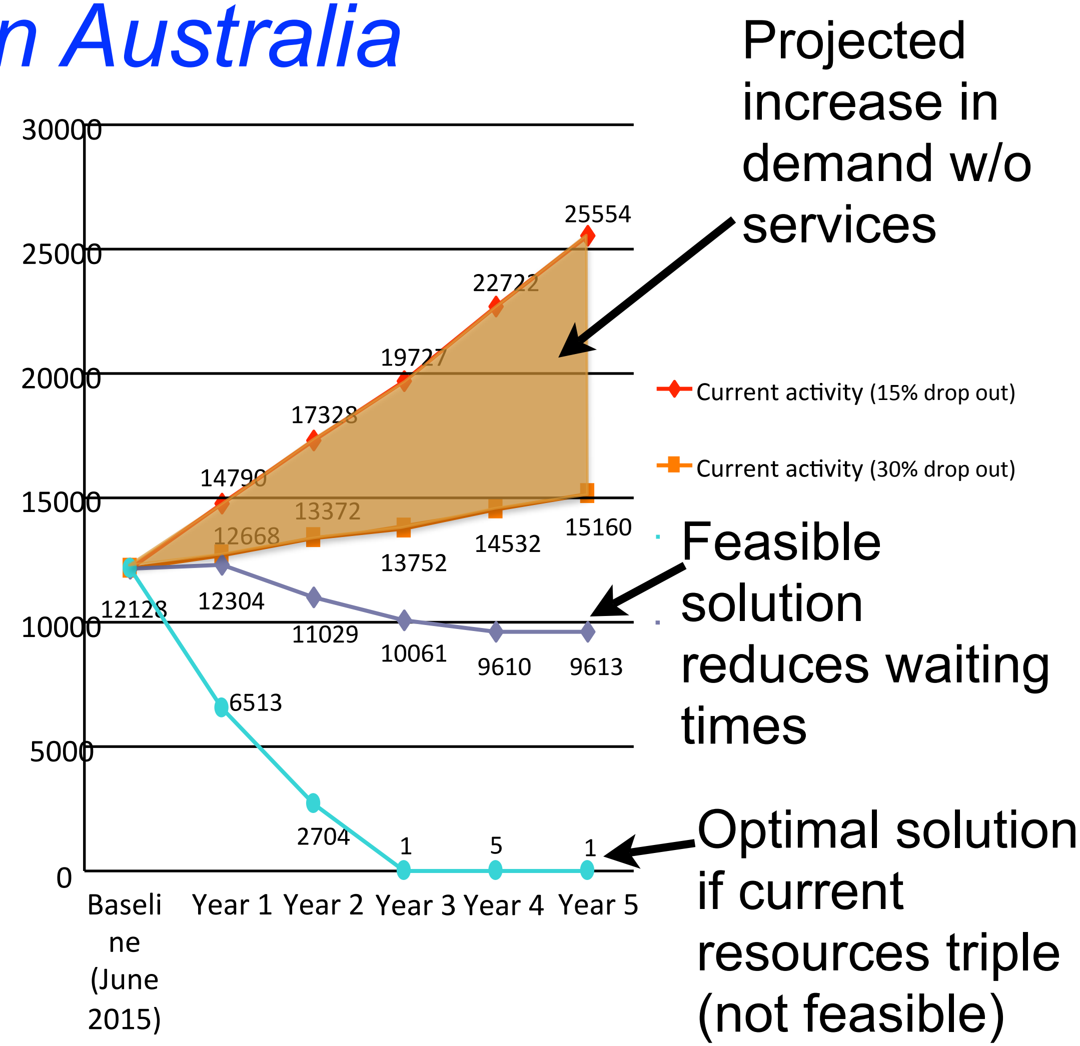
- An intervention's cost-effectiveness can vary by subgroup due to patient heterogeneity
- We use finite mixtures of disease activity models to identify relevant subgroups
- Characteristics of subgroups and their cost-effectiveness inform decisions on resource allocation.



Tracy Comans (Griffith University, Australia)

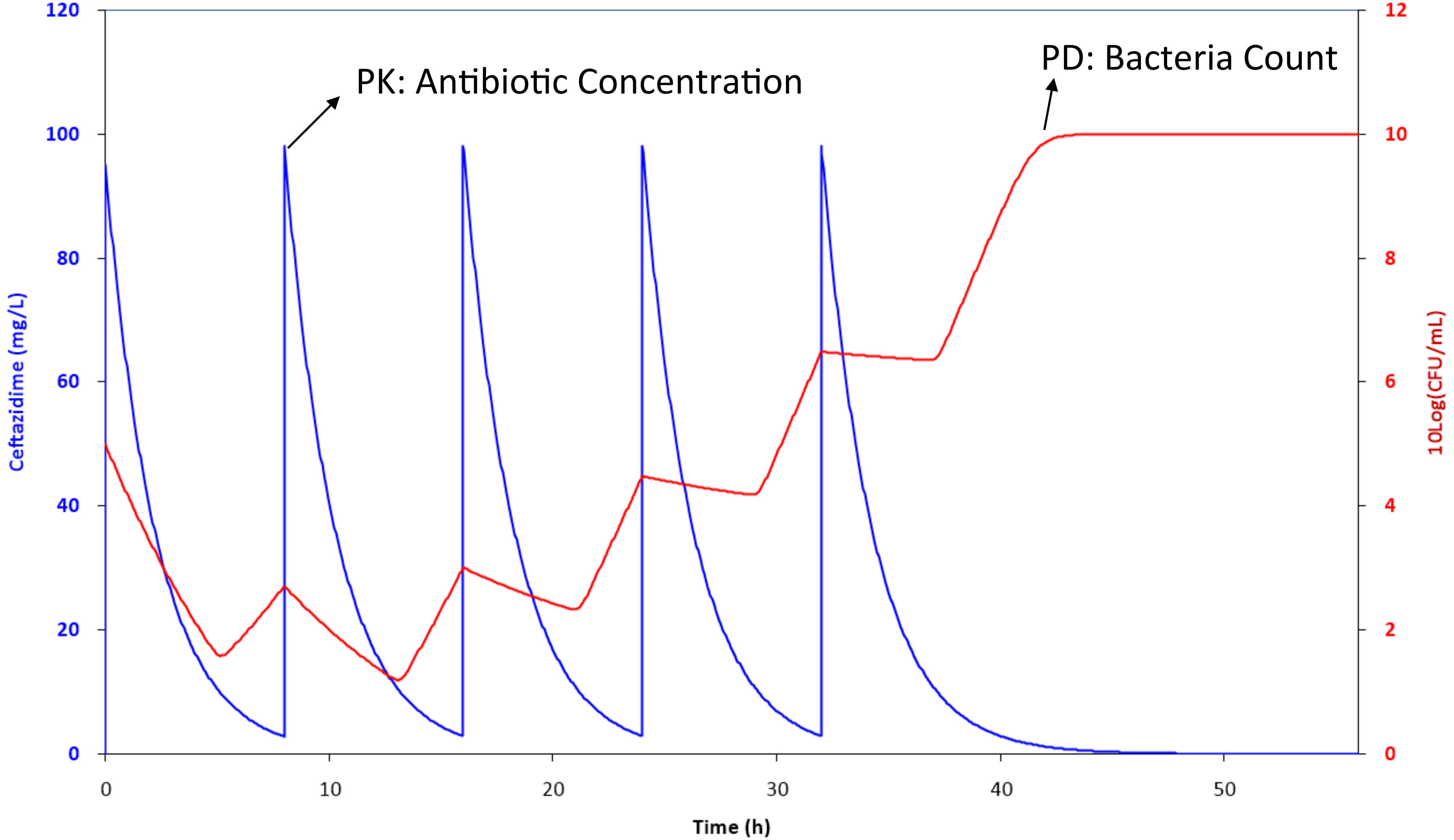
Estimating demand for orthopaedic specialist services in Australia

- Identify the gap between demand and service capacity
- Identify patients who would be suitable for physiotherapy-led management
- Develop recommendations to address current and future gaps in services.



Neiko Punt (Medimatics, The Netherlands)

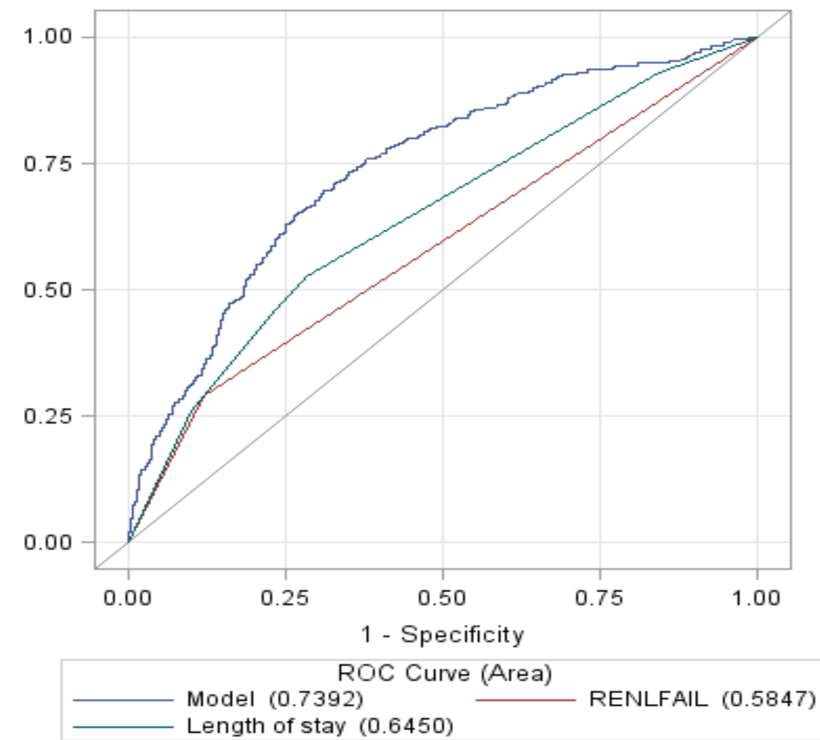
Visual PKPD Modelling Using EDSIM++



Carl Asche (University of Illinois, USA)

Identifying Acute Myocardial Infarction Patients at Risk for 30-Day Readmission

- We use routine electronic medical record data to identify acute myocardial infarction patients at risk of 30-day readmission
- Input: 3,058 AMI admissions at OSF HealthCare
  - a multi-site healthcare service where the average 30-day readmission rate was 8.9%

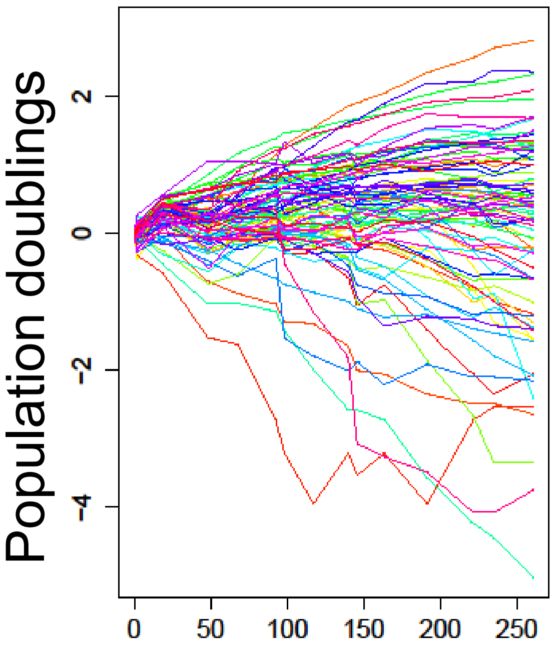


- Multi-level interventions could be tailored to individual readmission risk.

Bishal Paudel (Vanderbilt University)

Modelling Clonal Competitions and Phenotypic State Transitions

- Existing clonal heterogeneity drives an initial drug response
- However, all clones converge to a similar phenotypic state of balanced death and division
- Cancer cell subpopulations respond differently to drugs
- In repsonse to drugs, cancer cells transition through epigenetic states, ultimately settling in favourable attractor states.



Clonal variability in drug response measured as population doublings over time

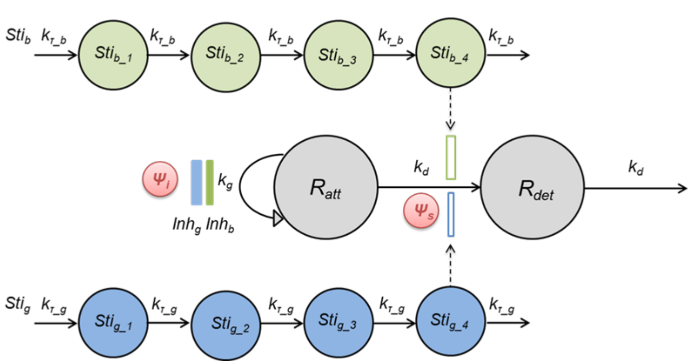
William J. Jusko (University of Buffalo, USA)

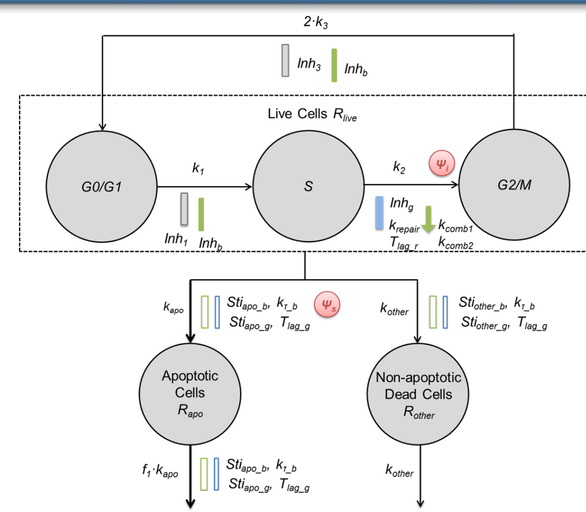
Chemotherapy Systems Modelling

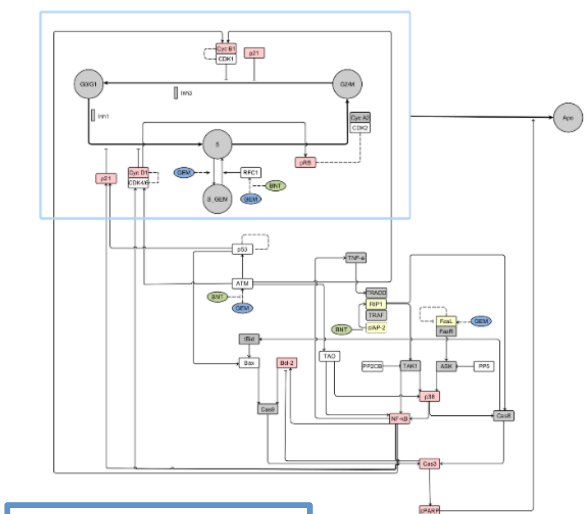
Evaluation & Optimization of combination therapy
Drug-focused

Biological system-focused
Exploration of drug MoAs and underlying system

Basic PD Model → **Mechanism-Based PD Model** → **Network Model**







Cell culture studies

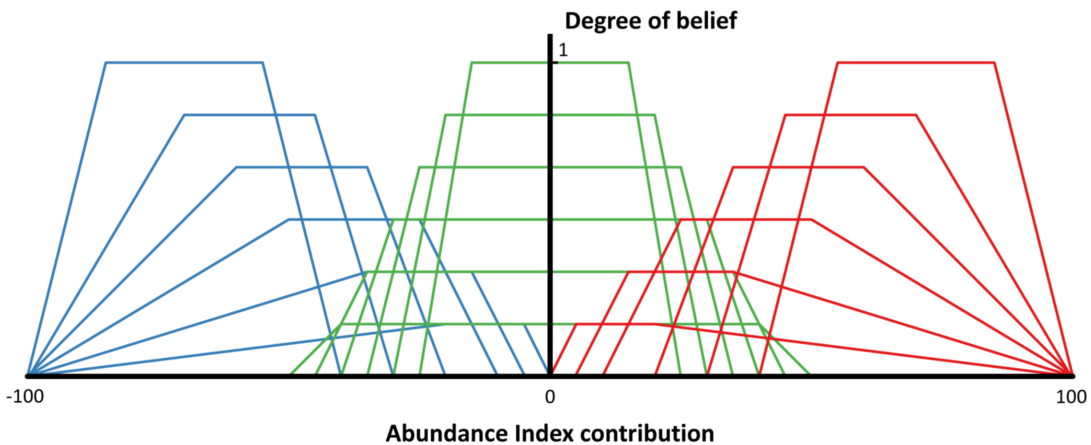
Assessing cell-cycle drug effects

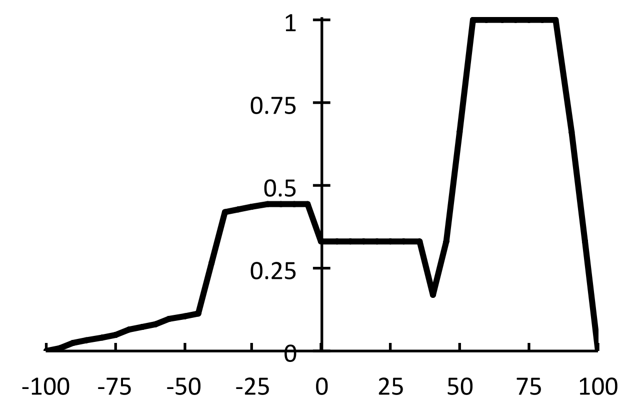
Genomic and proteomic studies

New targets or combinations for evaluation

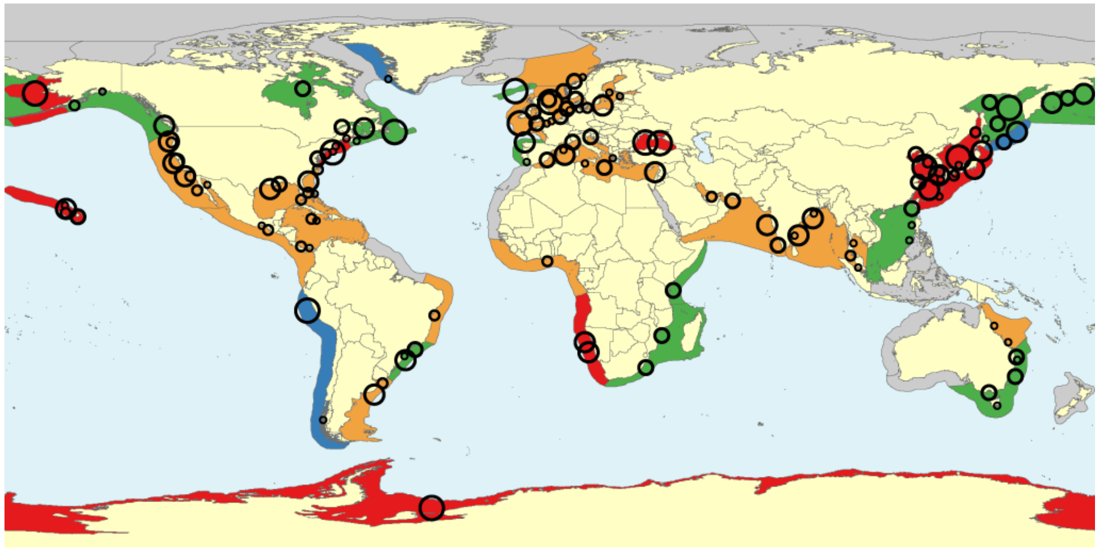
Lucas Brotz (University of British Columbia, Canada)

Examining population trends using fuzzy logic





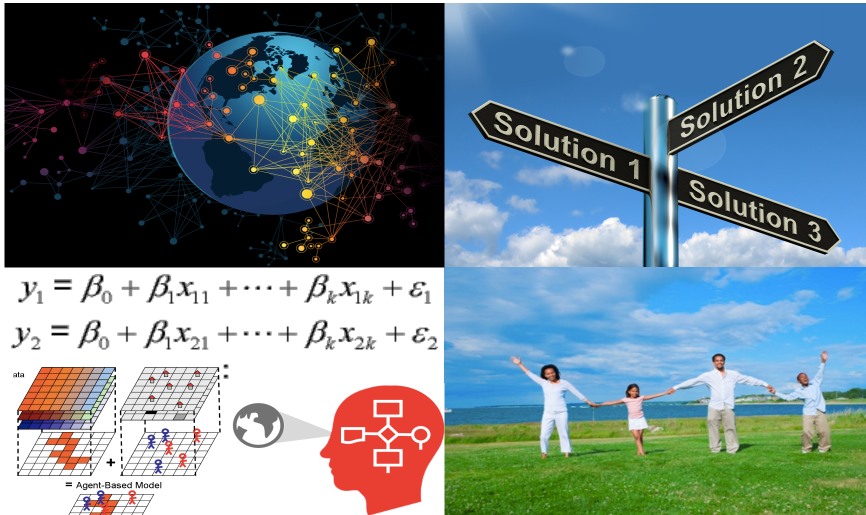
- Fuzzy logic represents variables according to a degree of membership
- Applied to global jellyfish populations
- Suggests populations are increasing in coastal ecosystems



Ayaz Hyder (Ohio State University, USA)

Systems Science in Epidemiology

- Systems science methods integrate data, develop explanatory models and evaluate solutions for better outcomes
- Eg agent-based models of influenza spread
- Microsimulation models for cost-effectiveness of cancer surveillance
- Satellite-based predictions for air pollution exposure and risk of birth outcomes.



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Discussion

- Through heterogeneous examples, we illustrate how the field has been conceptualised and evolved
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- We see a range of applications and tools
- Yet there is also unity, with a focus on utilising computation and theoretical methods as tools for tackling a multitide of problems
- We posit an alternate, two-dimensional view:

Contributor	Disease spread	Resource allocation	Drug effects	Risk assessment	Ecosystem management	Testing theory	Epidemiology/ Public health	Methods
Robert Smith?	x		x				x	Impulsive DEs, Latin hypercube sampling
Bruce Y. Lee	x						x	ABMs
Aristides Moustakas	x							ABMs
Andreas Zeigler				x				Random forests, support-vector machines
Mélanie Prague	x		x				x	ODEs, control theory
Romualdo Santos		x			x			Difference equations
Matthias Chung						x		Point-estimator methods for ODEs
Robin Gras					x	x		ABMs, fuzzy maps
Valery Forbes				x		x		Matrix models, ABMs
Sixten Borg		x	x				x	Finite mixtures, cost-effectiveness analysis
Tracy Comans		x					x	Discrete event simulation, cost-effectiveness analysis
Yifei Ma	x	x					x	Network models, diffusion dynamics
Neiko Punt			x					PKPD modelling, Bayesian estimates
William Jusko			x			x		PKPD modelling, ODEs
Lucas Brotz					x	x		Fuzzy logic analysis
Ayaz Hyder		x		x		x	x	ABMs, microsimulation models

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- Gathering large amounts of data in one place opens that data up to susceptibility on an unprecedented scale
- This can be a force for good or a massive privacy violation.

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- A growing challenge is the melding of the physical sciences with the social sciences
- If human behaviour is to be understood, modelling must draw upon fields that have expertise in the qualitative understanding of social, cultural and behavioural norms
- This cross-disciplinary understanding is necessary to improve our quantitative models.

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- The project continues...