Systems Biology Approaches in Radiation Health Research

Francis A. Cucinotta
University of Nevada Las Vegas
Las Vegas, NV 89154


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• **Systems Biology:**
  – Describes biological processes in terms of molecules, pathways, cell lineages, etc. in user defined manner. Typically multi-scale.
  – Involves computational and mathematical modeling of complex systems.

• **Systems Radiation Biology:**
  – Application of SB in study of radiation effects.
  – Radiation perturbation of biological systems and processes.

• **Translational Systems Radiation Biology:**
  – Risk prediction at low dose based on scientifically sound extrapolation of experiments.

Adapted from Vodovitz et al PLoS Comp Biol
Systems Biology of Systemic Immunity

Spitzer et al Cell (2017)
Spitzer et al Cell (2017)
Mathematical Realizations

Figure. Comparison of modeling results with experimental data: fraction of lymphocytes (dendritic cells, T eff, T help, T reg, NK cells and B cells) of (A) untreated, (B) ineffective anti-PD1 and (C) effective CD1 alloIgG treated samples, (D) differences in T cells in these conditions, and (E) tumor size of untreated versus ineffective and effective treated samples.
Kinetics Models of Biological Effects

- Biological systems evolve with time.
- After irradiation this evolution is perturbed due to DNA damage, ROS and altered signal transduction.
- There are a variety of mathematical approaches to describe the kinetics of biological responses:
  - Deterministic models based on Ordinary Differential Equations (O.D.E) describing sequences of binding, phosphorylation, etc.
  - Stochastic models:
    - Chemical Master equations
    - Monte-Carlo methods
  - Ad-hoc models such as Agent based models
- Spatial dependences by PDF or Monte-Carlo methods.

Bartocci and Lió (2016)
Mass-action Equation

• The law of mass action in chemical kinetics states that the rate at which a chemical is produced is proportional to product of reactants.

• Concentration of reactants A is written \([A]\).

• If A and B react to form C: \(A + B \rightarrow C:\)

\[
\frac{d[C]}{dt} = k[A][B]
\]

• For reaction \(A + B \leftrightarrow C\)

\[
\frac{d[A]}{dt} = k_{-1}[C] - k_1[A][B]
\]
\[
\frac{d[B]}{dt} = k_{-1}[C] - k_1[A][B]
\]
\[
\frac{d[C]}{dt} = -k_{-1}[C] + k_1[A][B]
\]

• The order of the reaction is important for understanding the process and character of solutions.
Mass-Action Equations- continued

- For more general reaction-
m, n, p are stoichiometric constants

\[ A + mB \xrightarrow{k} nB + pC \]

\[
\begin{align*}
\frac{dA}{dt} &= -kAB^m \\
\frac{dB}{dt} &= (n - m)kAB^m \\
\frac{dC}{dt} &= pkAB^m
\end{align*}
\]

- Stability analysis starts by setting all differentials to zero and considering the algebraic structure of the system for different values of the rate-constants (eq. linear, quadratic, cubic eq’s).

- For large biochemical systems- many coupled differential equations will occur. Rate-Constants are analogous to cross-sections in transport codes. Estimated from different experiments or calculated with mol. structure codes (CHARM, etc.).
Stochastic Approaches

- Stochastic approaches include Molecular Dynamics, Chemical Master equation (CME), Fokker-Plank or Monte-Carlo simulations.
- In CME, the Master equation is

\[
\frac{\partial P(x, t | x_0, t_0)}{\partial t} = \sum_{j=1}^{M} [a_j(x - \nu_j)P(x - \nu_j, t | x_0, t_0) - a_j(x)P(x, t | x_0, t_0)]
\]

- \(X(t)\) is the system state-vector at time \(t\), and \(a_j(x)\) is the “Propensity function” which describes probability of reaction \(j\) in time interval from \(t_0\) to \(t\).
- Stochastic approaches difficult for large systems, but can lead to distinct solutions from O.D.E. approach.
- Most common methods to solve CME is Gillespie’s method.
Modular Systems Biology: The complexity of biological systems suggests a Modular framework

Modules in Cancer Development

- Motility Circuits
- Cytostasis and Differentiation Circuits
- Hallmark capabilities

Modules in Neuronal Death

- Viability Circuits

Hanahan & Weinberg, Cell (2011)
Modular Systems Biology Terminology

• **Modularity of a System is Technique to reduce large system to several modules.**

• **Motifs:** elementary units in a Modular approach
  – E.g. single domain, interaction, etc.

• **Modules:** definition can be varied with application
  – E.g. group of interactions, clustered part of a network, a pathway, etc.
  – Block diagonalization of stoichiometric matrix describing interactions

• **Input/Output and Modules:** two biochemical systems, M1 and M2, have defined input and outputs. They can be considered modules when we can predict the behavior of the composite M12 from the input/output of M1 and M2 (Sauro, Mol Sys Biol, 2008).
Modular Systems Biology Terminology-continued

- **Retroactivity**: the effect a downstream process has on an upstream process.
  - e.g. negative feedback
- Modularity may also be predicted from molecular structures alone (Pawson et al. Science 2003).
- Non-equilibrium steady states and stability analysis.
- **Excitability**: The basal state is recovered after signals are removed.

Regulation of T-helper cells by retroactivity
TGFβ-Smad Pathway

- U. London Model (PNAS, 2008) describes Smad shuttling
- We added Radiation and Smad7 interactions along with Smad7 shuttling with Smurf interactions
- Detailed mathematical analysis of kinetics performed using Modularity concepts
- Stability theorems and solutions for system (Li et al. 2012)

### A. Stoichiometrix Matrix

The stoichiometric Matrix $S$ is given by

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Modular TGFβ – Smad Pathway

Stoichiometric Matrix

(Li, Wang, Carra & Cucinotta, 2012)
Stability analysis is made for each module simplifying overall analysis.

\[
\begin{align*}
\frac{dM_1}{dt} &= f_1(M_1, R, M_3) \\
\frac{dM_2}{dt} &= f_2(M_2, M_1) \\
\frac{dM_3}{dt} &= f_3(M_3, M_2)
\end{align*}
\]

**M1** - Regulation of TGFβ receptors (activated by IR and inhibited by Smad7/Smurf)
- \( \mathbf{Dr} \) (dose rate of IR), \( \mathbf{TGF}_p^L \) (latent TGFβ), \( \mathbf{TGF}_p^A \) (active TGFβ), \( \mathbf{S7f} \)
- \( \mathbf{R}_{\text{Inact}} \) (inactive TGFβ receptors), \( \mathbf{R}_{\text{Act}} \) (active receptors, bound by active TGFβ)

**M2** - Smad signaling (phosphorylation, degradation of Smad2, shuttling of Smad2,4)
- \( \mathbf{R}_{\text{Act}} \), \( \mathbf{S2} \) (Smad2), \( \mathbf{pS2} \) (phosphorylated Smad2), \( \mathbf{S4} \) (Smad4), \( \mathbf{S24} \) (Smad2-4)

**M3** - Synthesis of ubiquitin ligase (formation and shuttling of Smad7/Smurf)
- \( \mathbf{S24} \), mRNA7 (Smad7 mRNA), \( \mathbf{S7} \) (Smad7), \( \mathbf{S7f} \) (Smad7/Smurf)

(Li, Wang, Carra & Cucinotta, 2012)
Excitability is generated and inherited in the downstream signaling pathway.

TGFβ response to a periodic radiation source

(Li, Wang, Carra & Cucinotta, submitted 2011)
TGFβ and ATM Signaling: Retroactivity

• Kirschner et al. (Can Res. 2006) showed TGFβ regulates ATM responses in mammary epithelial cells using TGFβ null cells or inhibitors.
• We designed Experiment to test effects of ATM inhibition on classic TGFβ responses, with results suggesting retroactivity occurs.

Expression of EMT markers as a function of radiation dose, with or without the exposure to TGFβ in Mv1Lu cells, as well as the effect of ATM inhibitor (10µM ku55933)
Low Dose Cognitive Risks

- Rodent experiments suggest risk of cognitive effects based on tests such as Novel Object Recognition (NOR) and spatial memory tests.
- Meta-analysis reveals a log-normal distribution of responses with threshold dose near 1 rad.
- Low dose detriments to neuron morphology and chronic inflammation leading mechanisms for damage.
Biophysics of Neuron Degradation
Figure IA. Schematic representation of computer simulation of neuronal dendrite formation.
Summary

• Systems Biology using a Biochemical kinetics to describe radiobiology:
  – A variety of approaches exist based on deterministic and stochastic (usually Monte-Carlo models).
  – Spatial dependence of cells and tissue components and how the spatial dependence evolves with time including radiation induced changes.

• Radiation perturbs biological systems forming substrates for enzymatic transitions.

• Initial damage is linear with dose-dose-rate, however thresholds appears in responses.
  – Damage substrates- DNA, oxidative damage sites, etc.

• Systems of equation formulated based on presumed interactions and theoretical considerations.

• Excellent opportunities for experimentalist and theorists to interact.