Mechanism-Based Irreversible Pharmacodynamic Models

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Pharmacodynamic (PD) models describe a host's pharmacologic response resulting from drug-target interactions and are key in drug development. The pharmacologic effects may be reversible or irreversible; the difference lies in the system's response once the drug has cleared. Once the drug is eliminated from the system, a reversible response will recede concurrently, whereas an irreversible response will persist well beyond drug elimination. Irreversible effects are less straightforward in their mechanisms, and current models mimic this with slow-resolving kinetics instead of with signaling mechanisms that can induce irreversibility. In the present work, we propose mechanisms that describe drug modes of action able to generate irreversible PD effects. We hypothesize a core signaling cascade incorporating an ultrasensitive response, thus generating irreversible hysteresis and bistability. Combined with a basic pharmacokinetic model, we propose PD models utilizing this core cascade able to induce irreversible effects via a) acute (single dose) exposure; b) multiple, lower strength exposures; and c) chronic, lowest strength exposure. The PD models outlined here can emulate these conditions and provide plausible mechanisms for their inductions of irreversible effects. Additionally, the models can be applied outside the field of drug development and to the long-term effects of stress, such as the physiological damage of chronic stress-induced allostatic load. Supported by NIH R25ES020721 and the Rutgers University SURF Program.