Computational Analysis of Uncoordinated Physiological Closed-Loop Controlled Critical Care Devices:

A Fluid Resuscitation-Intravenous Anesthesia Case Study

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Acknowledgment, Disclosure, and Fundings

Acknowledgment

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Isolated PCLC Design, Simultaneous Clinical Use

PCLC = Physiological Closed-Loop Control

Isolated Control Design

Fluid Resuscitation Loop:

BP controller — **BP**

Blood Pressure

Propofol Infusion Loop:

Anesthesia controller — **BIS**

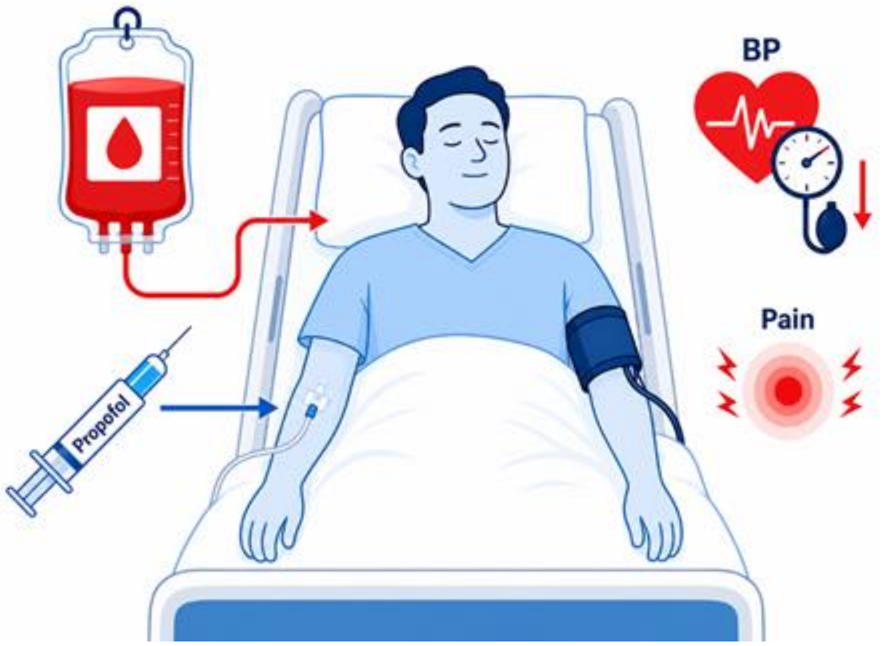
Bispectral Index [0, 100]; a measure of depth of anesthesia

Our Case Study

Core Question

What happens when independently designed PCLC operate simultaneously?

Integrated Patient Physiology



MECHANISTIC COUPLING

Multiple Closed-Loop Treatments Can Interact with Each Other

BIS rise / light anesthesia

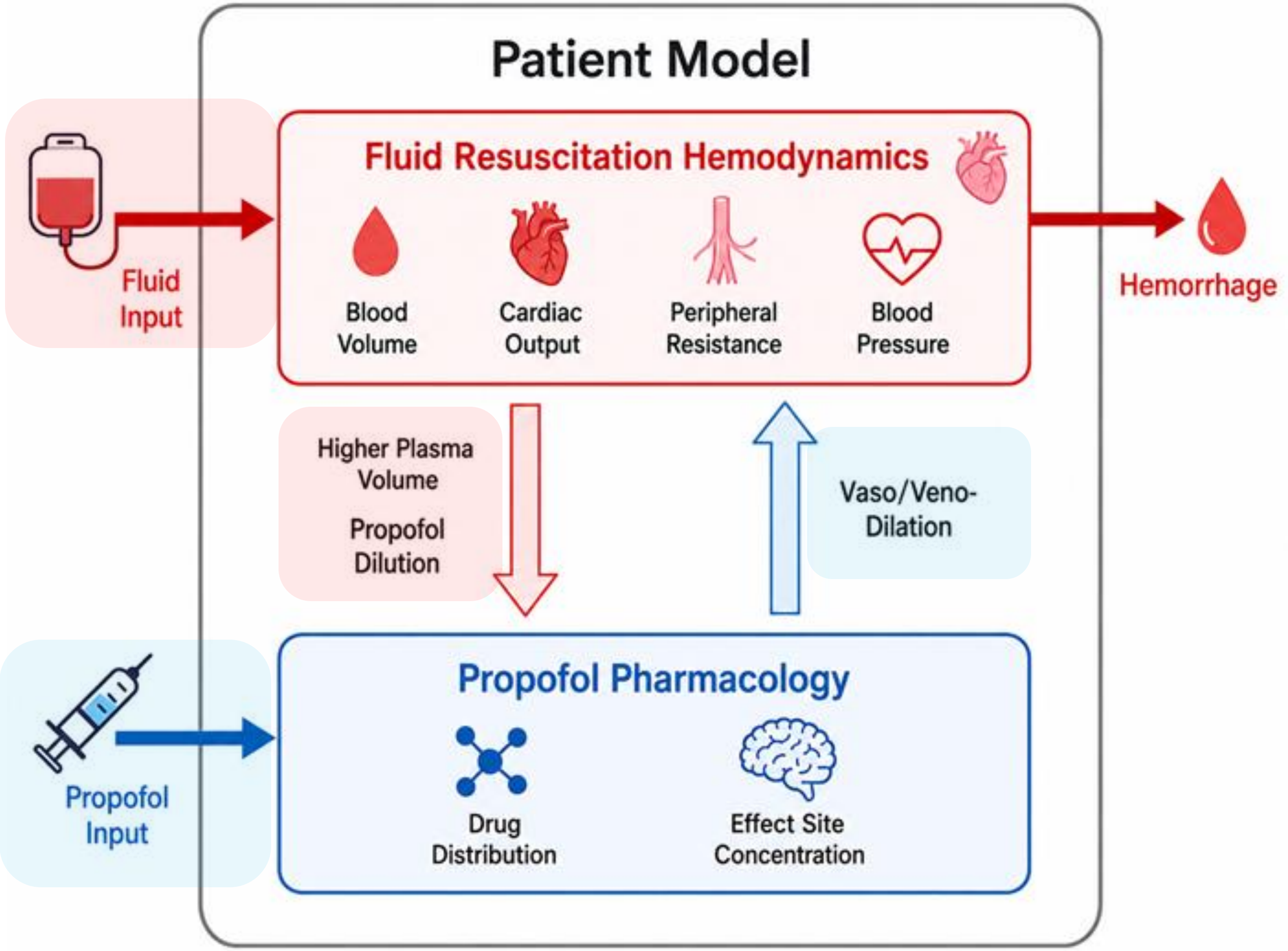
Interaction 1: Propofol Dilution

Drug effect ↓ ⇒ BIS ↑

Hypotension

Interaction 2: Vaso/Veno-Dilation

TPR ↓ ⇒ BP ↓



Key message: **Isolated control design may not account for the patient's integrated physiological response.**

How Can We Analyze Interaction Behavior in Simultaneous CL Treatments?

Computational Analysis Pipeline

Combined Monte-Carlo Steady-State and Dynamic Reachability Analysis

1) Steady-State Reachability

Safe Destination

Is the target a feasible equilibrium point that can be maintained without violating physiological limits?

Equilibrium

Constraints:

- ✅ CO<CO_max
- ✅ TPR<TPR_min

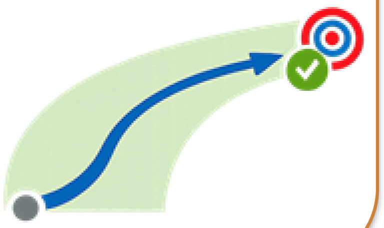
2) Dynamic Reachability

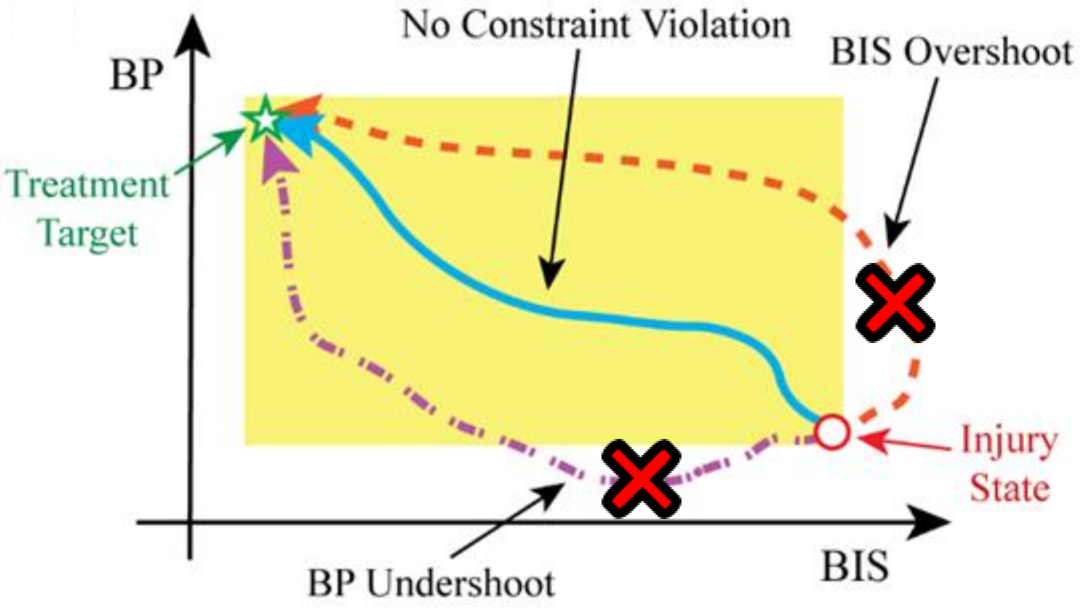
Safe path

Can the patient move toward the target without unsafe Transient behavior?

Constraints:

- ✅ CO,
- ✅ TPR,
- ✅ BP,
- ✅ BIS,





Key message: Target Reachability = Steady-State + Dynamic Reachability

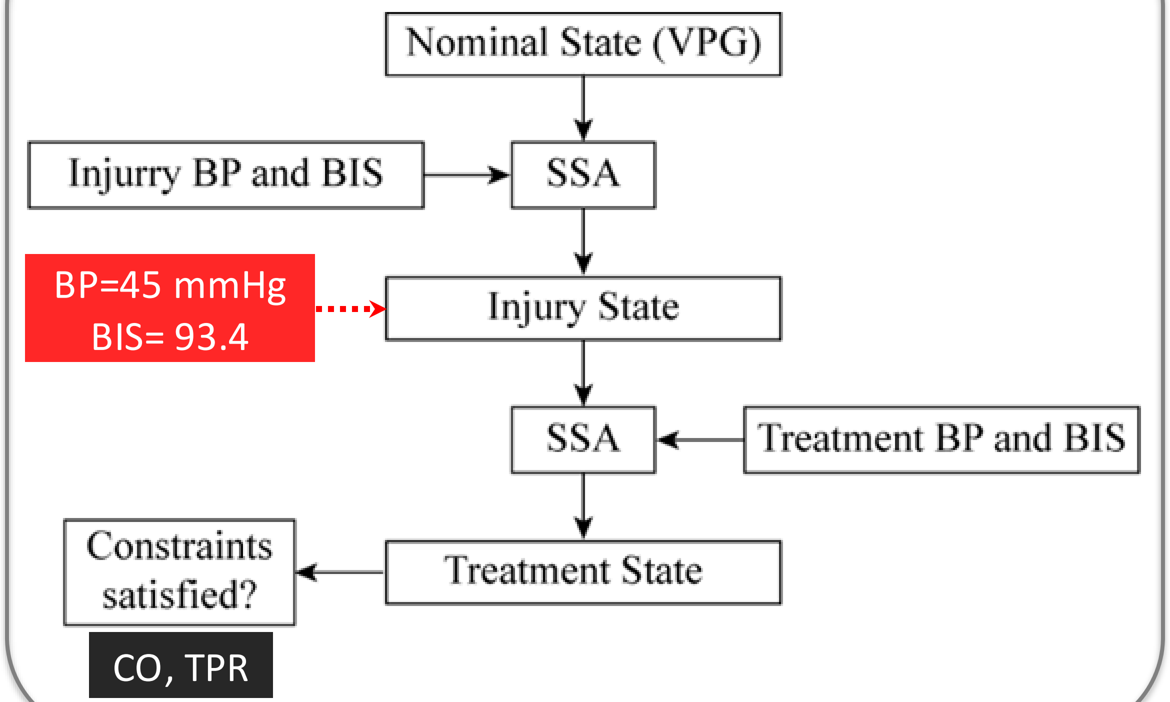
Step #1: Steady-State Reachability

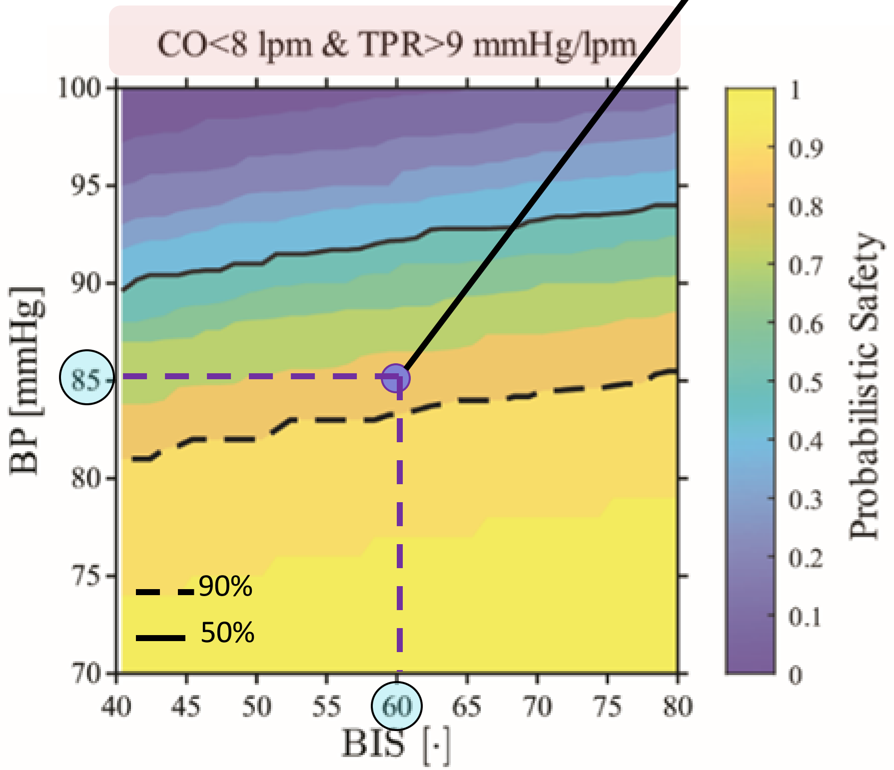
VPG = Virtual Patient Generator
SSA = Steady-State-Analysis

Steady State Analysis

Chosen Target:
BP = 85 mmHg and BIS = 60

Static Reachability Percentage: 86%





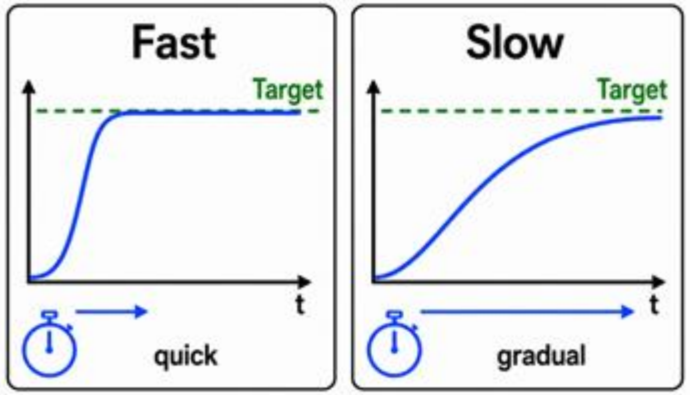
Finding 1: Not all treatment targets are reachable without violating physiological constraints

[1] Tivay et al., "Collective variational inference for personalized and generative physiological modeling: A case study on hemorrhage resuscitation," IEEE TBME, 2021.

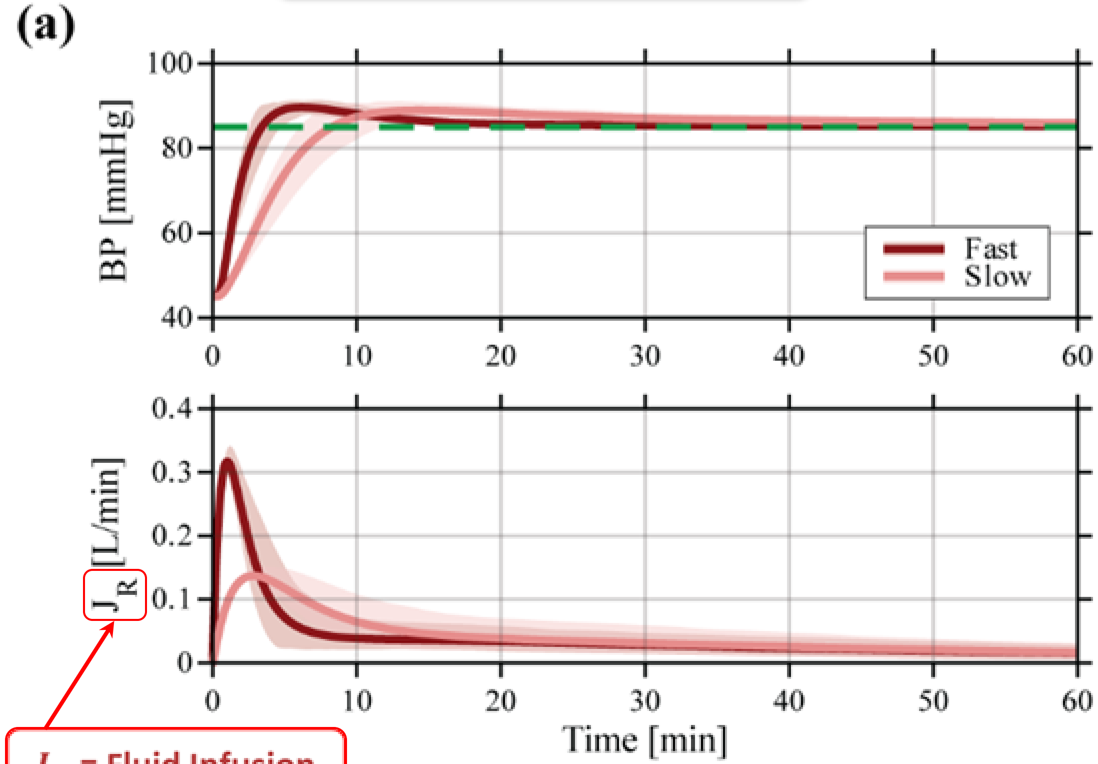
SISO Controllers Applied Separa

SISO = Single Input Single Output

Fast and **Slow** controllers are implemented to apply **different combination** of **controllers for examining Dynamic Reachability**

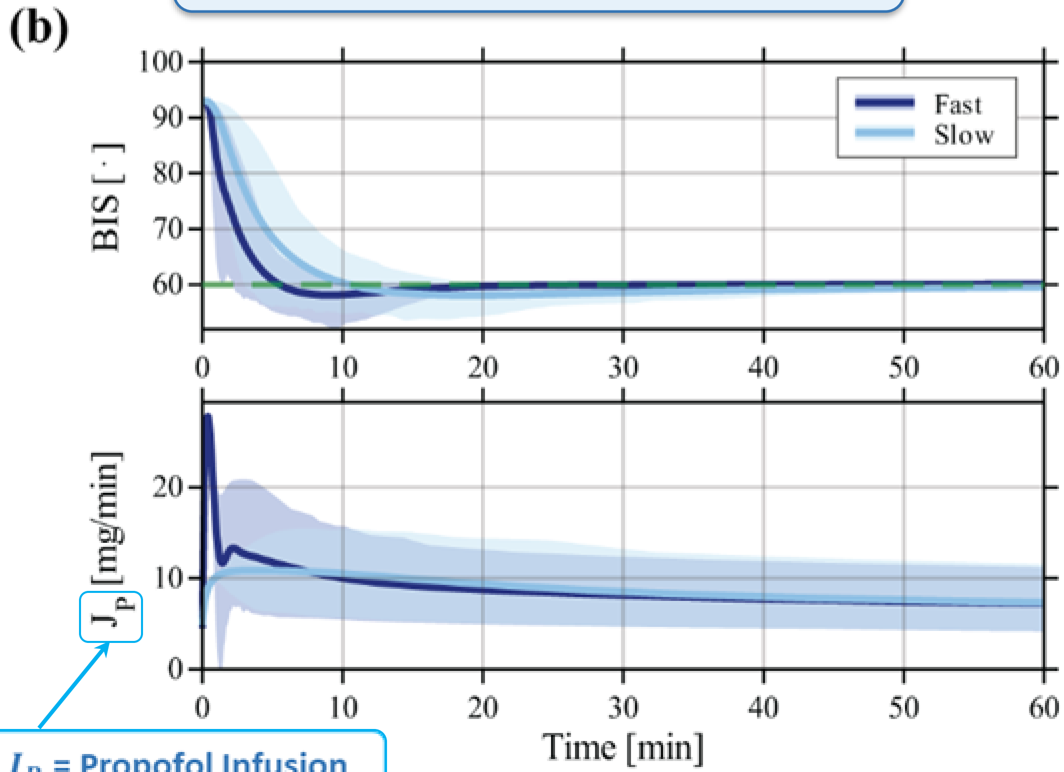


BP Controller in Isolation



J_R = Fluid Infusion

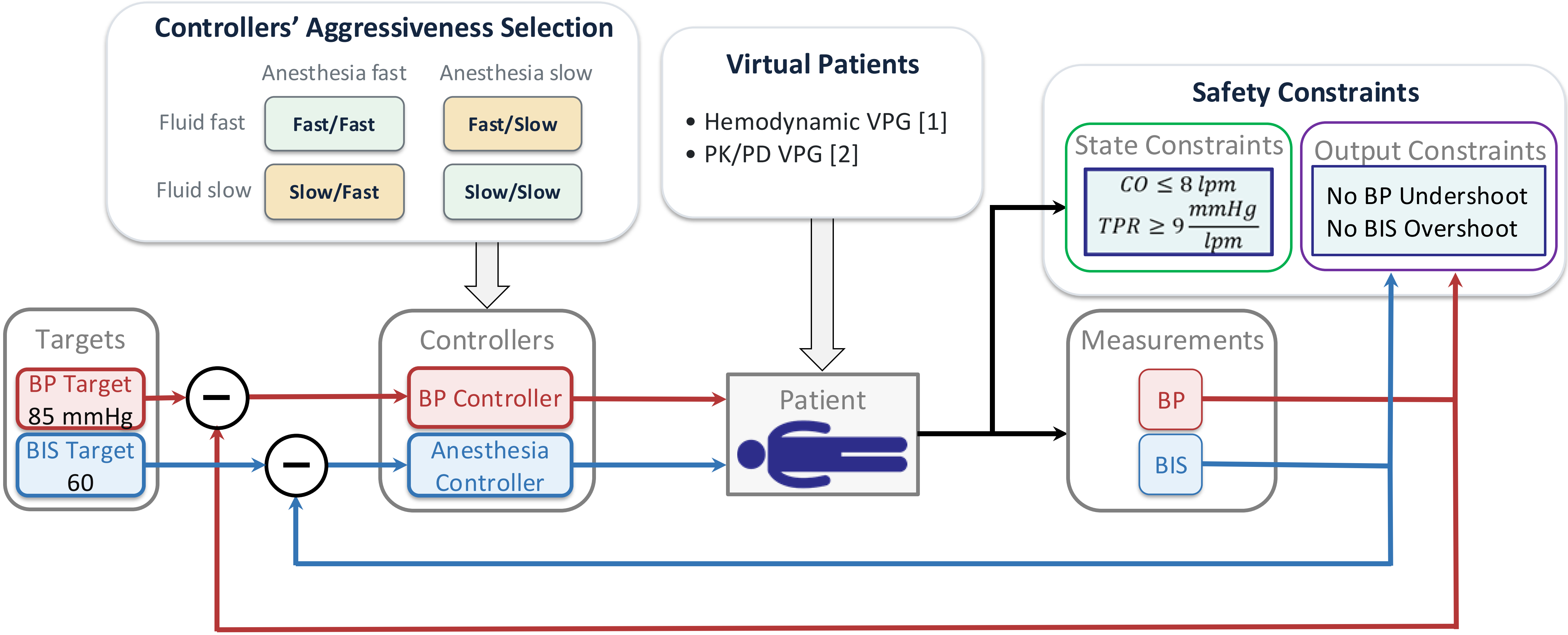
Anesthesia Controller in Isolation



J_P = Propofol Infusion

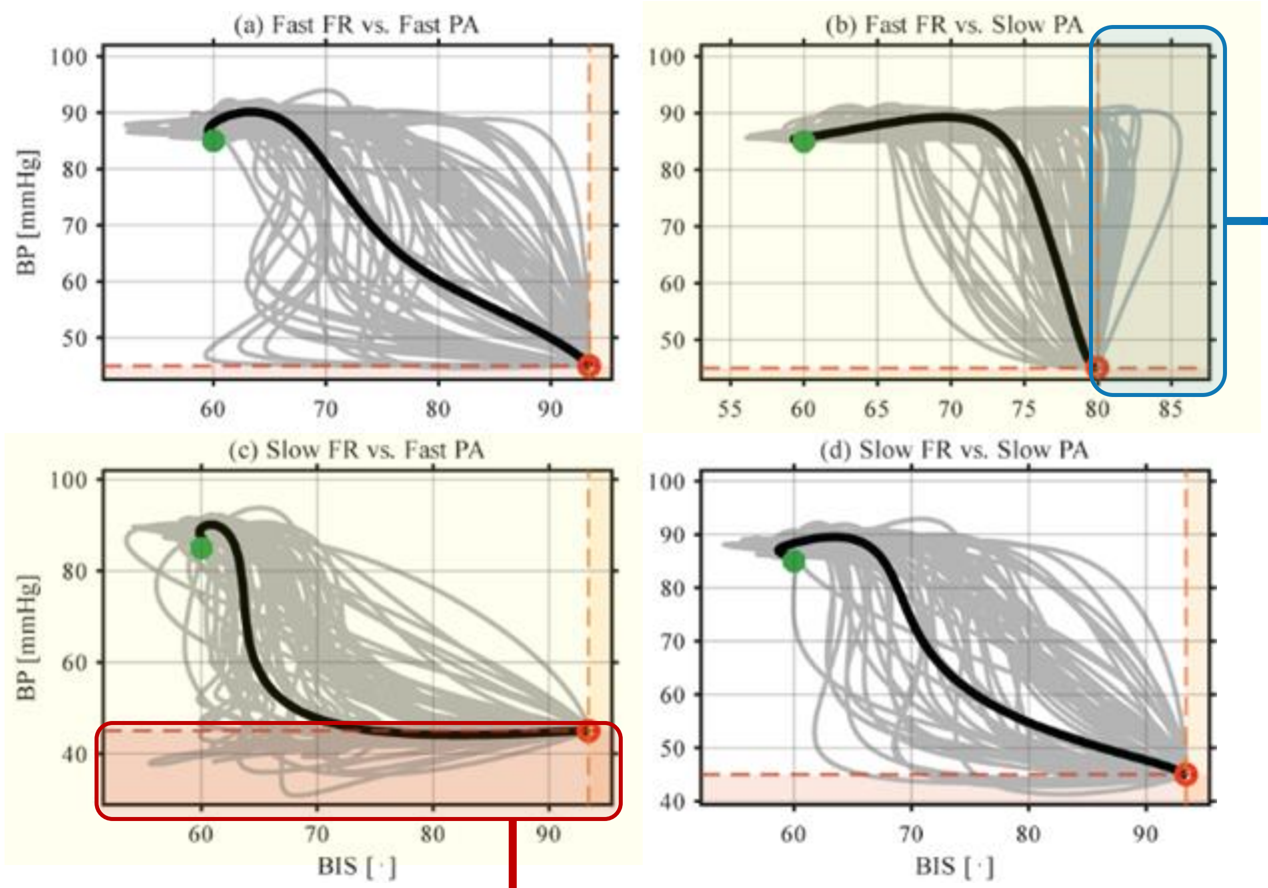
Step #2: Dynamic Reachability

Dynamic simulation considering patient variability, controller aggressiveness, and constraints:



[2] Eleveld et al., "Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation," Br. J. Anaesth., 2018.

Step #2: Dynamic Reachability



Fast Fluid Resuscitation + Slow Anesthesia

- Aggressive volume restoration can dilute propofol faster than the anesthesia loop compensates
- **Observed concern:** transient **BIS overshoot**

Slow Fluid Resuscitation + Fast Anesthesia

- Aggressive anesthesia can cause vaso/veno-dilation before the resuscitation loop compensates
- **Observed concern:** transient **BP undershoot**

Step #2: Dynamic Reachability

Steady State Analysis

Chosen Target: BP = 85 mmHg and BIS = 60

Steady-State Reachability Percentage: 86%

Controller pair BP/BIS	BP violation	BIS violation	CO violation	TPR violation	Combined violation	Dynamic Reachability
F / F	2 %	0 %	16 %	13 %	18 %	**82%**
F / S	0 %	23 %	23 %	21 %	40 %	**60%**
S / F	**59** %	0 %	18 %	14 %	66 %	**34%**
S / S	19 %	0 %	19 %	14 %	34 %	**66%**

Some Comparisons

- Controller **with** matched aggressiveness performed **better**
- Controller **without** matched aggressiveness performed **worse**

Finding 2: Even steady-state reachable targets can exhibit transient violations of prescribed constraints

Finding 3: The situation can get worse with larger mismatch in control aggressiveness

Implication: Closed-Loop Treatment Needs to Be Verified Before Deployment

Engineering Implication (Development)

- Closed-loop treatments should not be evaluated only in isolation
- Relative controller aggressiveness should be treated as a system-level design variable
- Supervisory monitoring may help detect transient violations

Clinical Implication (Field Use)

- Multiple closed-loop treatment controllers should be used with care
- Additional physiological measurements may be needed to ensure the safety of patients
- Simulation can identify risky scenarios before field use

Limitations

- Although the underlying mathematical models have been validated, the findings of this study have not been clinically validated.
- Controllers were designed for safety analysis, not optimized for clinical deployment
- Generalizability to other treatments are not investigated

Reachability Analysis Pipeline For Closed-Loop Treatment Controller

Take-Home Message

- Good performance in isolation does not guarantee good performance when controllers are used together.
- Independently developed closed-loop treatments can interact and create unsafe conditions, especially when their response speeds are mismatched.
- In-silico reachability analysis can identify risky operating scenarios before deployment.

Practical conclusion

Future closed-loop systems should be evaluated as interacting treatment systems, not as isolated controllers.

Thank you

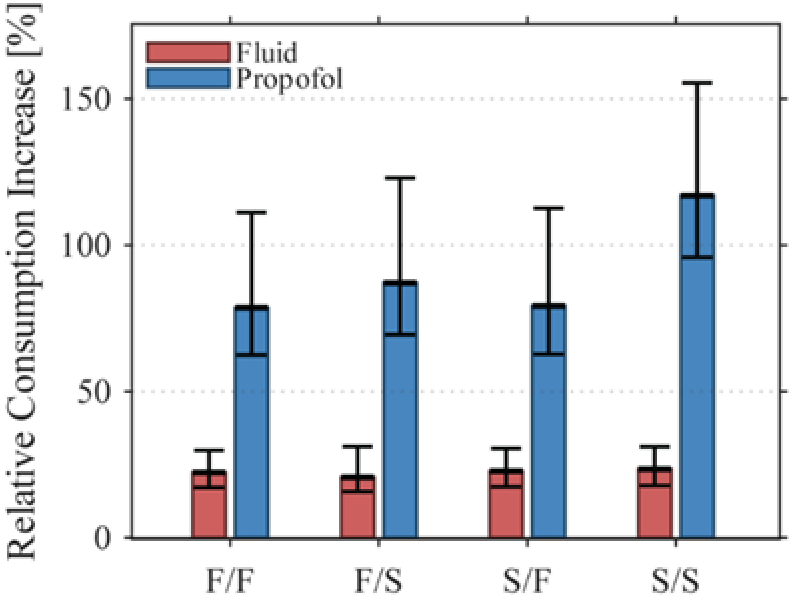
Step #2: Dynamic Reachability

Fluid Use

≥20% median increase
relative to individual fluid-resuscitation control

Propofol Use

≥75% median increase
relative to individual anesthesia control



Interpretation

- The two control loops may act against each other rather than coordinate.
- Higher propofol usage may be associated with transient violation of CO/TPR
- Higher fluid consumption may contribute to CO overshoot.

Finding 4: Fluid and drug usage increased in simultaneous treatment scenarios versus individual treatment