Solution Report

Prepared by the MitPlan Group
(Malvika Rao, Martin Michalowski, Szymon Wilk, Wojtek Michalowski)

Part 1: Architecture and Use

- *Architecture: Please provide a diagram illustrating the system architecture and briefly explain its components.*

  Figures 1, 2, and 3 show an overview of the architecture and main execution steps.

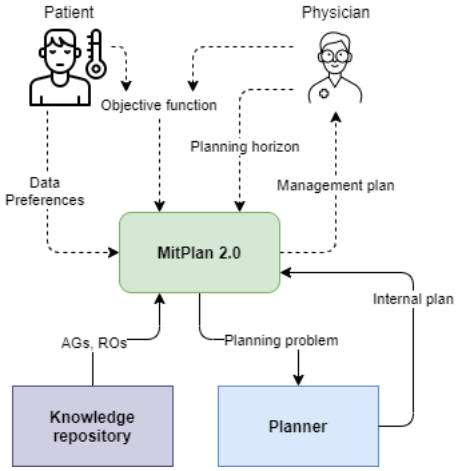

Figure 1: Architecture of MitPlan 2.0

input : data: patient data, prefs: patient preferences, horizon: planning horizon, objFunc: objective function for plan optimization
output: managementPlan: management plan

1 AGs := select from **knowledge repository** extended AGs representing CPGs used to manage the patient
2 ROs := select from **knowledge repository** revision operators possibly applicable to AGs
3 problem := create a planning problem using AGs, ROs, data, prefs, horizon and objFunc
4 internalPlan := apply **planner** to problem to find an optimal plan
5 managementPlan := post-process internalPlan to management plan
6 return managementPlan

Figure 2: Pseudo-code with operations of MitPlan 2.0

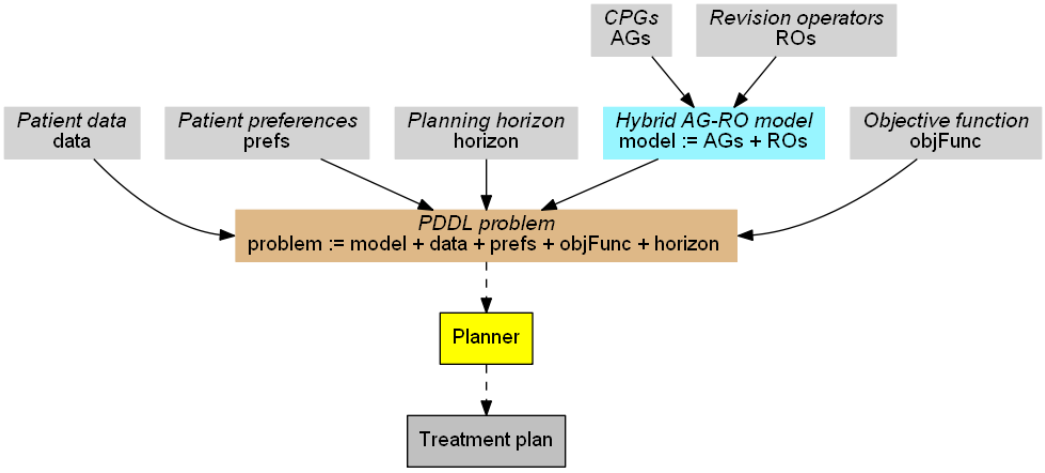

Figure 3: Overview of representation and processing in MitPlan 2.0

MitPlan 2.0 is invoked for a specific patient-physician encounter and takes patient data, patient preferences, a planning horizon, and multivariate objective function as input. The objective function (weights and metrics) can be defined in advance or during patient physician encounter. We assume that there are two knowledge repositories – one with the CPGs and the other with knowledge about adverse interactions (generic and specific for a given disease) and we encode the later knowledge in a formal construct called the *revision operator* (RO). Patient data (recorded diagnosis) tells the approach what CPGs to be retrieved from the knowledge repository and what are potential revision operators that deal with possible adverse interactions. For our approach, each CPG in the repository is represented as an *actionable graph* (AG) – more explanation later – and all applicable to a patient encounter AGs are combined with potentially applicable revision operators to create a hybrid model, called the *hybrid AG-RO model* (see below for more details).

MitPlan 2.0 combines the patient data, patient preferences, a planning horizon, an objective function and the hybrid AG-RO model (or AG-RO model in short) to create a planning problem instance, encoded in PDDL, that is fed to the planner. We use the OPTIC planner for this purpose. The code consists of a single domain file, common to all use cases, that defines the set of actions needed to solve the problem, and one problem file that encodes each use case. The focus of our approach is on representation – that is, how to represent and encode the planning problem as well as the input data so that a planner can find the optimal treatment plan. Once the mitigation problem is represented as a planning problem, the processing and reasoning is left entirely to the OPTIC planner to carry out. The planner uses the encoded problem instance to output an internal plan, if one exists, which is then filtered to remove low-level implementation details. The final output is a treatment plan presented to the patient and the physician.

Our approach allows us to make use of a multivariate objective function that supports a combination of multiple clinical dimensions. In the current implementation, the objective function minimizes a weighted sum of user-identified metrics, where the weights are chosen to reflect metrics' relative importance. The weights can be adjusted and and the metrics can

be customized for a specific patient encounter. MitPlan 2.0 is capable of addressing different decision making priorities via changes to the objective function, making our approach flexible and scalable.

When metrics are not defined, MitPlan 2.0 still assigns an "execution cost" to each action node in the AG-RO model, and optimizes with respect to the default objective function – it finds the plan that minimizes total cost. Patient preferences are handled via costs (an alternative preferred by a patient is set to be less costly in the AG-RO model). Action nodes introduced by revision operators to mitigate adverse interactions are assigned a higher cost than the original action nodes in the AG that they revise. Such a design ensures the planner always selects the original action node unless an adverse interaction makes it necessary to opt for a revising action node instead. A revision operator may indicate multiple action nodes equally suitable for replacing original action node associated with an adverse interaction. In this instance, the planner prioritizes the revising action node that is less costly (this may be due to patient preference or some other factor). Because the hybrid AG-RO model unifies and captures all information pertinent to revisions and preferences, the planner can optimize over various alternative plans, selecting the plan associated with the lowest cost.

Next we define some terminology used in our work. *Clinical actions* are activities related to patient treatment as defined in the disease-specific CPG and represented in its corresponding AG. *Planning actions* are components of the PDDL planning task, defined in the domain file, that specify ways to change the state of the world. They represent clinical actions and all other state manipulations needed to find a treatment plan. When associated with a duration, they are referred to as temporal planning actions. A *clinical goal* is a node in the AG that, when reached, signifies that the treatment requirements for that disease have been satisfied. The clinical goal can be a terminal node in the AG when treatment planning is to be exhaustive, or it can be a node placed somewhere between diagnosis and a terminal node to capture a pre-defined treatment planning horizon. A *planning goal* is a specification of what state we want the world to be in once the found plan is executed. In our CPG mitigation problem formulation, the planning goal is a conjunction of the goal nodes across all relevant disease-specific AGs with an optional objective function.

- *CIG representation: Please explain the formalism used to represent CPGs.*

  A CPG is represented as an actionable graph (AG) which consists of action, decision, and goal nodes. We assume that there are alternative action nodes so patient preferences can be defined (if such alternatives do not exist, then it is not possible for a patient to have a preference). Patient data on preferences indicate which of these alternative actions a patient prefers for any given treatment.

  A revision operator (RO) takes the form of a logical rule, consisting of triggering conditions and mitigating actions. RO supports replacement of an action node in the AG that triggers an adverse interaction, the deletion of an action node in the AG, or the addition of a new action node.

  A hybrid AG-RO model consists of two components: i) the AGs expanded to include nodes introduced by ROs that are applicable to the present AGs and ii) the triggering sequence that identifies the presence of an adverse interaction, and which set of nodes comprise this interaction.

A triggering sequence is encoded as a binary vector of length equal to the number of nodes in the hybrid AG-RO model. Each vector element indicates whether the corresponding node is part of the revision sequence. An adverse interaction is present only if a particular plan includes all action nodes present in a revision sequence. Since adverse interactions must be mitigated, the planner searches for an alternate plan, one that does not contain all the action nodes from the revision sequence. Rather, an alternate plan contains action node that replaces the node in the triggering sequence associated with the adverse interaction (e.g., action node "prescribe SCB" that replaced action node "prescribe PCB").

Thus, the hybrid AG-RO model is a unified representation that fully captures the AG, including any alternative nodes required to support preferences, as well as revision operators and associated nodes required for revisions. For a patient encounter, MitPlan 2.0 combines the input data (patient values, preferences, costs, metrics, and objective function) with the hybrid AG-RO model and invokes the planner to find the optimal treatment plan.

- *Domain knowledge representation: If additional domain knowledge is required, please explain how it is represented. Indicate whether standards (e.g., SNOMED-CT, FHIR, standard domain ontologies) are being utilized.*

  Our approach does not rely on any specific standard. Rather, it is flexible and can accommodate any standard. It is up to the user/developer to decide on a standard as part of building the front-end of the system.

- *Mode of use: Please explain the intended mode of use of the system: who are the intended end-users, when is the system to be used: during patient encounter, real-time vs. simulation, etc.*

  The aim is to support treatment planning. During patient physician encounter, patient data is acquired, a treatment plan is generated for a given planning horizon (of any length). While our approach is designed to be used as an offline process during a patient encounter, it can also be embedded in a real-time or simulation system.

- *Strengths of the approach: Does the approach have very good support for particular features? Which? Please justify. What is the singular point of strength of your approach?*

  Our approach is flexible, scalable, and CPG agnostic. It enables the use of a multivariate objective function that captures the multi-dimensional nature of treatment and provides flexibility to address different clinical goals. It also supports time horizons that define how far into the future we want to plan a patient's treatment. For a given patient encounter, different clinical goals can be achieved simply by changing the objective function components with no need to re-encode the problem.

  MitPlan 2.0 optimizes over the planning model and generates an optimal treatment plan, if one exists, in a single run, eliminating the need for procedural or algorithmic handling of interactions.

Part 2: Features

Section A. Interactions among CPGs' advice

A1: Drug from a CPG has an effect on a comorbid condition
For example, low-dose Aspirin (Cardiovascular Disease CPG) affects Duodenal Ulcer (comorbid condition).

Implemented (Y/N): Y
Brief description: This is handled via ROs. The AG is expanded to include the additional nodes introduced by the revision operator to mitigate interaction. As well, a triggering sequence identifying the presence of the adverse interaction is defined. During execution the planner opts to visit the mitigating action nodes in order to produce an interaction-free plan (see use case 2).

A2: Two or more drugs from different CPGs interact
For example, antibiotics such as Trimethoprim/Sulfamethoxazole impact the anticoagulant effect of Warfarin.

Implemented (Y/N): Y
Brief description: See explanation above.

A3: Clinical goals from different CPGs conflict
For example, the goal of preventing thrombosis conflicts with the goal of preventing bleeding during surgery.

Implemented (Y/N): Implemented partially
Brief description: We interpret conflict between goals as conflict between actions. If there exists a mitigation strategy (e.g., one or more ROs) that involves resolution of such a conflict then the planner uses it to generate an optimal treatment plan. Without a mitigation strategy a treatment plan is not generated.

A4: Conflicting actions (e.g., drugs, procedures) from different CPGs
For example, one CPG recommends administration of Clopidogrel (Transient Ischemic Attack CPG) while another recommends suspending Clopidogrel (Coronary Artery Bypass Grafting CPG).

Implemented (Y/N): Y
Brief description: ROs and temporal planning actions enable us to address this issue. A drug may be suspended during a certain period and resumed later.

A5: Duplicate or redundant advice from different CPGs
For example, Calcium Channel Blockers are recommended in Hypertension and Cardiovascular Disease CPGs.

Implemented (Y/N): Implemented partially
Brief description: Duplicate or redundant advice can be represented by action nodes that are shared across different AGs. If explicitly stated, duplicate actions can be controlled, for example, via dosage

prescribed by each action. Otherwise, the planner does not automatically reconcile the duplication of actions. Duplicate actions must be identified and removed by post-processing of the internal plan.

A6: Temporal relationship between different CPGs
For example, take Cefpodoxime (Acute Otitis Media CPG) two hours after taking antacids (Gastroesophageal Reflux Disease CPG).

Implemented (Y/N): Y
Brief description: This is handled via temporal planning actions where we can specify the duration of the action.

A7: Multiple interactions from different CPGs interacting at the same time
For example, replacing low-dose Aspirin (Transient Ischemic Attack CPG) with Proton Pump Inhibitor to mitigate Duodenal Ulcer (Duodenal Ulcer CPG) impacts new comorbid condition of Osteoporosis (Osteoporosis CPG).

Implemented (Y/N): Y
Brief description: The planner handles secondary effects, assuming it knows how to mitigate them. This is supported via the revision operators represented in the hybrid AG-RO model, and via the planner's search for an optimal plan taking into account the objective function.

Section B. Mitigation strategies when CPGs offer interacting advice

A mitigation strategy is a meta-action taken to address one or many of the interactions that were identified above.

B1: Adding a drug to mitigate an adverse effect
For example, add a PPI to mitigate the Duodenal Ulcer due-to Aspirin.

Implemented (Y/N): Y
Brief description: ROs can introduce, remove and replace action nodes.

B2: Adjust drug dosage
For example, a reduction of 10% of warfarin dosage.

Implemented (Y/N): Y
Brief description: ROs can also employ functions that change certain characteristics of action nodes.

B3: Monitor the effect of a drug
For example, monitor progression of the Duodenal Ulcer during overlapping treatment with Aspirin.

Implemented (Y/N): Y
Brief description: This feature involves introducing a monitoring action (e.g., checking the INR level), and the planner can process this. It may also involves loops in the AG-RO model, which

the planner is able to handle with appropriate instructions for termination.

B4: Replacing a drug with a safer / non-interacting drug / more effective drug for comorbidity
For example, replace Aspirin with Clopidogrel for a patient with Duodenal Ulcer.

Implemented (Y/N): Y
Brief description: This is handled across multiple features. It is enabled via ROs, via patient preferences, and via the multivariate objective function (for example, a metric such as effectiveness can be used by the planner to find an optimal plan).

B5: Discard unsafe/interacting drug
For example, suspend ACE inhibitor when eGFR value drops by over 30% over 4 months.

Implemented (Y/N): Y
Brief description: ROs support the deletion of certain action nodes.

B6: Delay a task to avoid a temporal overlap
For example, stop Dabigatran 4 days prior to surgery for a patient with high bleeding risk.

Implemented (Y/N): Y
Brief description: This is handled via ROs and temporal planning actions.

B7: Add a task to ensure a temporal overlap
For example, for a patient with high risk of thromboembolism who is undergoing surgery with a high risk of bleeding, suspending Warfarin 5 days prior a surgery and resuming it one day after the surgery, introduces a 6-day period where the patient is at risk of bleeding; bridge with heparin starting on day 3 prior to surgery till the day of surgery to ensure overlap of the surgery context and the thromboembolism prevention context.

Implemented (Y/N): Y
Brief description: This is handled via ROs and temporal planning actions.

B8: Are there any other mitigation strategies for the multimorbidity CPG problem that you have implemented?

Implemented (Y/N): Y
Brief description: Our approach is able to select the optimal mitigation strategy, depending on criteria provided in advance. Thus we can employ several strategies to address a single problem.

Section C. Other features

C1: Patient preferences and/or patient burden
For example, choosing one drug over another due to lower price; or choosing DOACs over warfarin to avoid checking INR on regular basis.

Implemented (Y/N): Y
Brief description: Patient preferences and patient burden are supported by assigning costs to relevant actions and using a multivariate objective function (see use case 2).

C2: Optimization of clinical resources
For example, grouping tests on the same day.

Implemented (Y/N): Implemented partially
Brief description: Resources that are directly associated with the CPG (i.e., medications, "cost" of revisions, etc.) can be optimized by properly defining components of the multivariate objective function. However, optimizing resource utilization of certain kinds, such as combining tests into a single day, is considered to be outside the scope of a mitigation problem that is presented to a planner.

C3: Explanation of the mitigation strategy(ies)
For example, why a given strategy was identified and what it entails.

Implemented (Y/N): N
Brief description: Although the plan generated is descriptive, explanations are not provided.

C4: Alternative mitigation strategies for a single interaction
For example, if there are more than one possible mitigation strategies, are they identified and presented.

Implemented (Y/N): Implemented partially
Brief description: The planner returns one plan in a single run. However it gives us the ability to identify and select alternative plans by changing the objective function (and there is no need to re-encode the problem).

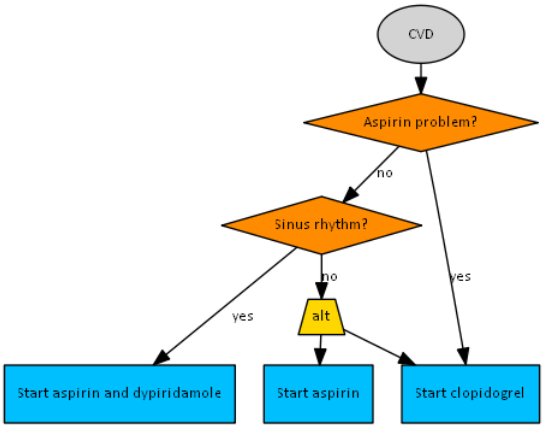

Figure 4: Actionable Graph for TIA

Part 3: Implementation of the Case Studies: Use Case 1

Input

The input to MitPlan 2.0 consists of the AGs derived from the CPGs corresponding to the diseases in the use case, and patient data. This use case does not specify any patient preferences or planning horizon. We do not need to make use of revision operators for this use case. No metrics are specified and the use case does not involve an objective function. Therefore, we use the default objective function with execution costs as described in Part 1. Figures 4, 5, and 6 depict the AGs for transient ischemic attack (TIA), duodenal ulcer (DU) and osteoporosis respectively. Figure 7 shows a sample of the code representing the AGs. The patient scenario and data are explained in the next section.

Processing

The encoding of a problem instance, processed by the planner, involves four main elements described next: patient data and preferences (including a planning horizon), interactions and revision operators, the hybrid AG-RO model, and the objective function.

Patient data and preferences

This use case describes the situation of a 76 year old woman diagnosed with TIA and DU, who subsequently developed osteoporosis in addition to her existing conditions. Our implementation allows all goals to be satisfied. Partial goals can also be met by appropriately specifying patient data and preferences. This use case involves the following features: A1, A7, B1, B4, B5, C1.

Interactions and revision operators

We do not need to make use of revision operators for this use case.

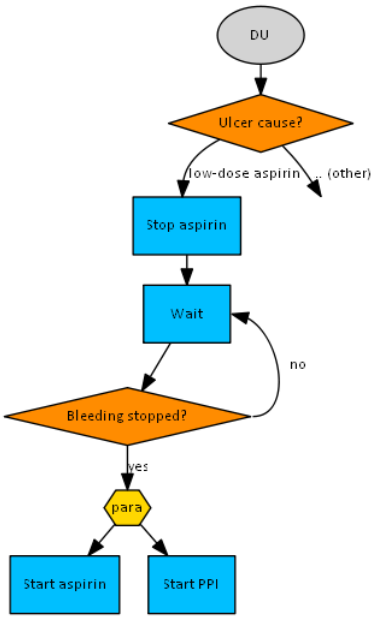

Figure 5: Actionable Graph for DU

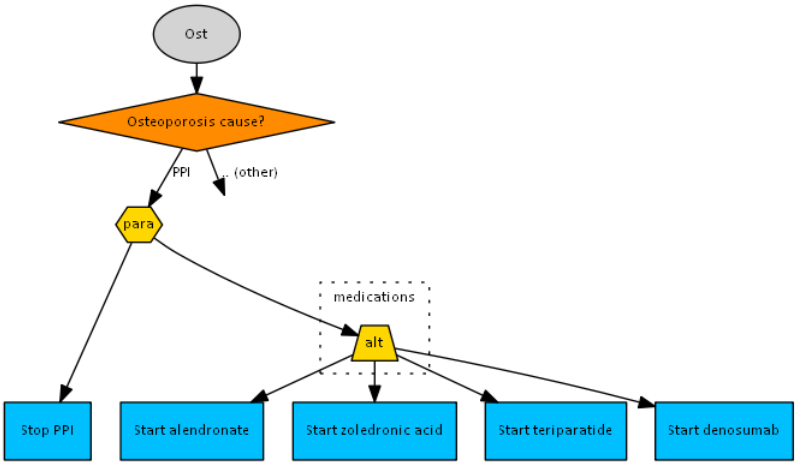

Figure 6: Actionable Graph for Osteoporosis

```
;;DU
(predecessorNode ULCERCAUSE_LOWDOSEASPIRIN G_DU)
(predecessorNode ULCERCAUSE_LOWDOSEASPIRIN STOPASPIRIN)
(predecessorNode STOPASPIRIN WAIT)
(predecessorNode WAIT BLEEDINGSTOPPED)
(predecessorNode BLEEDINGSTOPPED WAIT)
(predecessorNode BLEEDINGSTOPPED P1)
(predecessorNode P1 PSTARTASPIRIN)
(predecessorNode PSTARTASPIRIN PSTARTASPIRIN_END)
(predecessorNode P1 PSTARTPPI)
(predecessorNode PSTARTPPI PSTARTPPI_END)
(predecessorNode PSTARTASPIRIN_END P2)
(predecessorNode PSTARTPPI_END P2)
(predecessorNode P2 G_DU)

(decisionNode ULCERCAUSE_LOWDOSEASPIRIN)
(decisionNode BLEEDINGSTOPPED)
(actionNode STOPASPIRIN)
(actionNode WAIT)

(parallelStartNode P1)
(parallelEndNode P2)
(parallelActionNode PSTARTASPIRIN)
(parallelActionNode PSTARTASPIRIN_END)
(parallelActionNode PSTARTPPI)
(parallelActionNode PSTARTPPI_END)


;;OSTEO
(predecessorNode OSTEOCAUSEPPI STOPPPI)
(predecessorNode OSTEOCAUSEPPI G_OSTEO)
(predecessorNode STOPPPI ALTNODE_OSTEO)
(predecessorNode ALTNODE_OSTEO STARTALENDRONATE)
(predecessorNode ALTNODE_OSTEO STARTZOLEDRONIC)
(predecessorNode ALTNODE_OSTEO STARTTERIPARATIDE)
(predecessorNode ALTNODE_OSTEO STARTDENOSUMAB)
(predecessorNode STARTALENDRONATE G_OSTEO)
(predecessorNode STARTZOLEDRONIC G_OSTEO)
(predecessorNode STARTTERIPARATIDE G_OSTEO)
(predecessorNode STARTDENOSUMAB G_OSTEO)

(decisionNode OSTEOCAUSEPPI)
(decisionNode ALTNODE_OSTEO)
(actionNode STOPPPI)
(actionNode STARTALENDRONATE)
(actionNode STARTZOLEDRONIC)
(actionNode STARTTERIPARATIDE)
(actionNode STARTDENOSUMAB)


;;TIA
(predecessorNode ASPIRINPROBLEM SINUSRHYTHM)
(predecessorNode ASPIRINPROBLEM STARTCLOPIDOGREL)
(predecessorNode SINUSRHYTHM ALTNODE_TIA)
(predecessorNode SINUSRHYTHM STARTASPDYPI)
(predecessorNode ALTNODE_TIA STARTASPIRIN)
(predecessorNode ALTNODE_TIA STARTCLOPIDOGREL)
(predecessorNode STARTASPDYPI G_TIA)
(predecessorNode STARTASPIRIN G_TIA)
(predecessorNode STARTCLOPIDOGREL G_TIA)

(decisionNode ASPIRINPROBLEM)
(decisionNode SINUSRHYTHM)
(decisionNode ALTNODE_TIA)
(actionNode STARTCLOPIDOGREL)
(actionNode STARTASPDYPI)
(actionNode STARTASPIRIN)
```

Figure 7: Code representing AGs for use case 1

Hybrid AG-RO model

The hybrid AG-RO model for this use case is the same as the AGs of the three diseases. Because there are no revision operators, the AGs are not expanded to include any new nodes, and there are no triggering sequences.

Objective function

The planner minimizes total execution cost since no metrics are specified for this use case. Execution costs are explained in Part 1.

Output

The planner is run on the domain file and the use case problem file, and an optimal treatment plan is generated. The planner outputs an internal plan that can be easily post-processed to remove details of the execution of the planner and the final treatment plan is presented to the patient and physician. Figure 8 shows the internal plan generated by the planner for this use case.

```
0.000: (makefirstdecision d_osteo osteocauseppi stopppi)  [0.000]
0.000: (makefirstdecision d_du ulcercause_lowdoseaspirin stopaspirin)  [0.000]
0.000: (makefirstdecision d_tia aspirinproblem sinusrhythm)  [0.000]
0.001: (makedecisiontodecisionnode d_tia sinusrhythm altnode_tia)  [0.000]
0.002: (takeactiontodecisionnode d_osteo stopppi altnode_osteo)  [0.000]
0.002: (takeactiontoactionnode d_du stopaspirin wait)  [0.000]
0.002: (makedecisiontoactionnode d_tia altnode_tia startaspirin)  [0.000]
0.003: (makedecisiontoactionnode d_osteo altnode_osteo startalendronate)  [0.000]
0.004: (takeactiontogoal d_tia startaspirin g_tia)  [0.000]
0.004: (takeactiontodecisionnode d_du wait bleedingstopped)  [0.000]
0.005: (makedecisiontoparallelblock d_du bleedingstopped p1)  [0.000]
0.005: (takeactiontogoal d_osteo startalendronate g_osteo)  [0.000]
0.006: (finalgoalreached d_tia g_tia)  [0.001]
0.007: (finalgoalreached d_osteo g_osteo)  [0.001]
0.007: (takeparallelactionnorevisions d_du p1 pstartppi pstartppi_end)  [0.000]
0.007: (takeparallelactionnorevisions d_du p1 pstartaspirin pstartaspirin_end)  [0.000]
0.010: (exitparallelblocktogoal d_du p2 g_du)  [0.000]
0.012: (finalgoalreached d_du g_du)  [0.001]
```

Figure 8: Internal plan for use case 1: TIA, DU, Osteoporosis

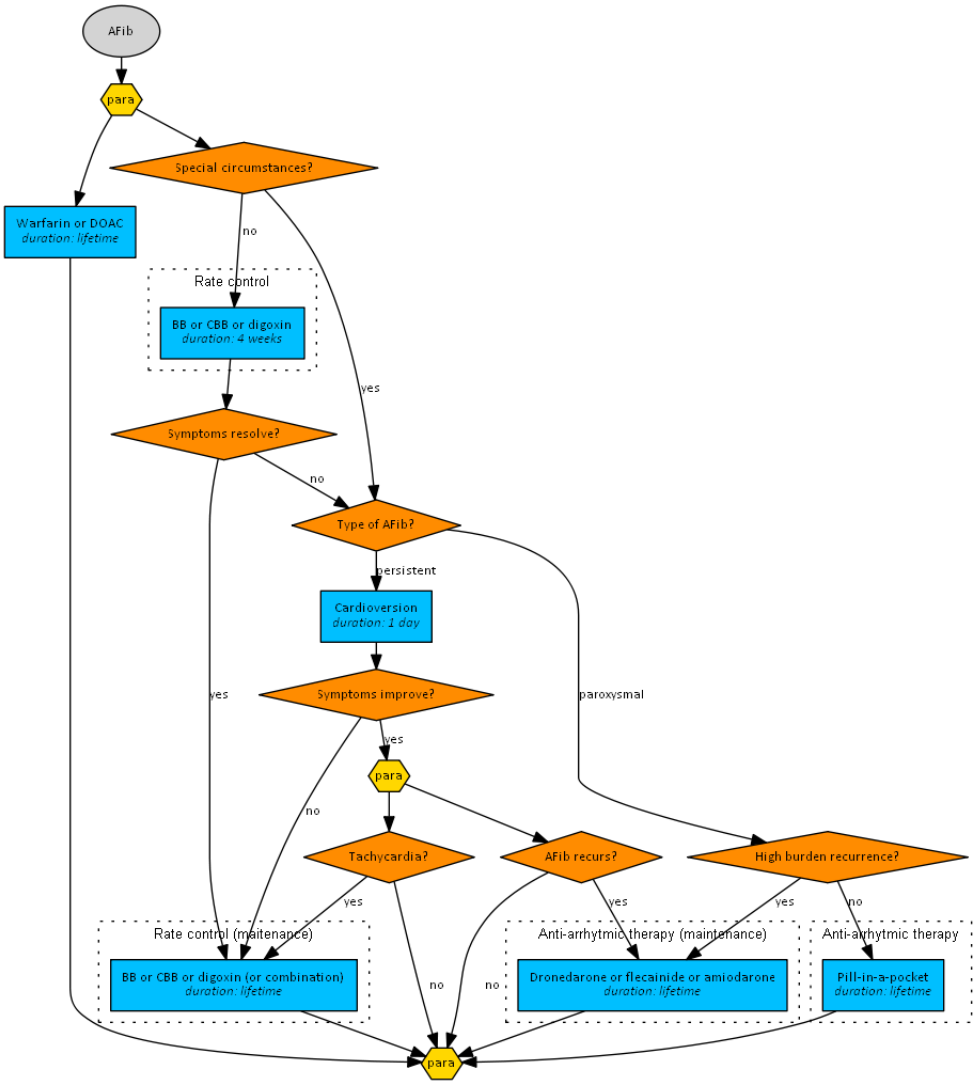

Figure 9: AG for AFib

Part 3: Implementation of the Case Studies: Use Case 2

Input

The input to MitPlan 2.0 consists of the AGs derived from the CPGs corresponding to the diseases in the use case, patient data and preferences, a planning horizon, revision operators, information regarding costs and other metrics, and the objective function to obtain an optimal plan that is relevant to the use case. Figures 9, 10, and 11 depict the AGs for atrial fibrilation (AFib), hypertension (HTN), and chronic kidney disease (CKD) respectively. The patient scenario and input data are explained in the next section.

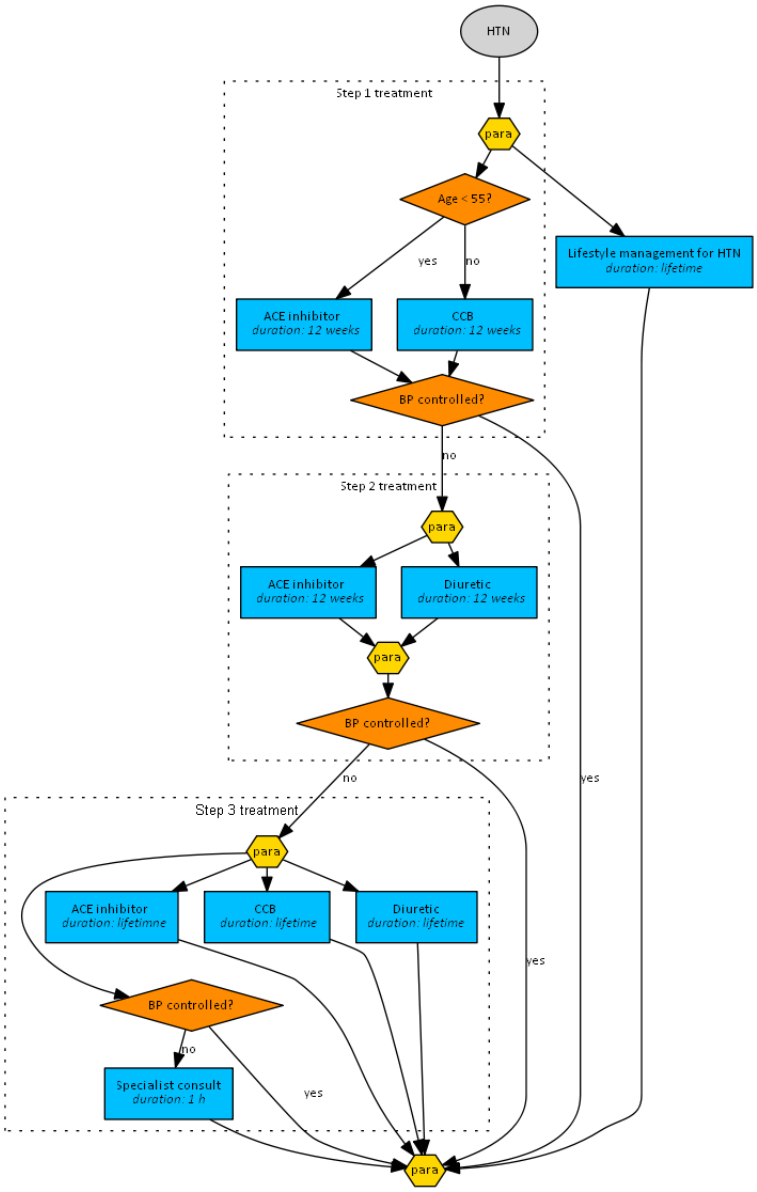

Figure 10: AG for HTN

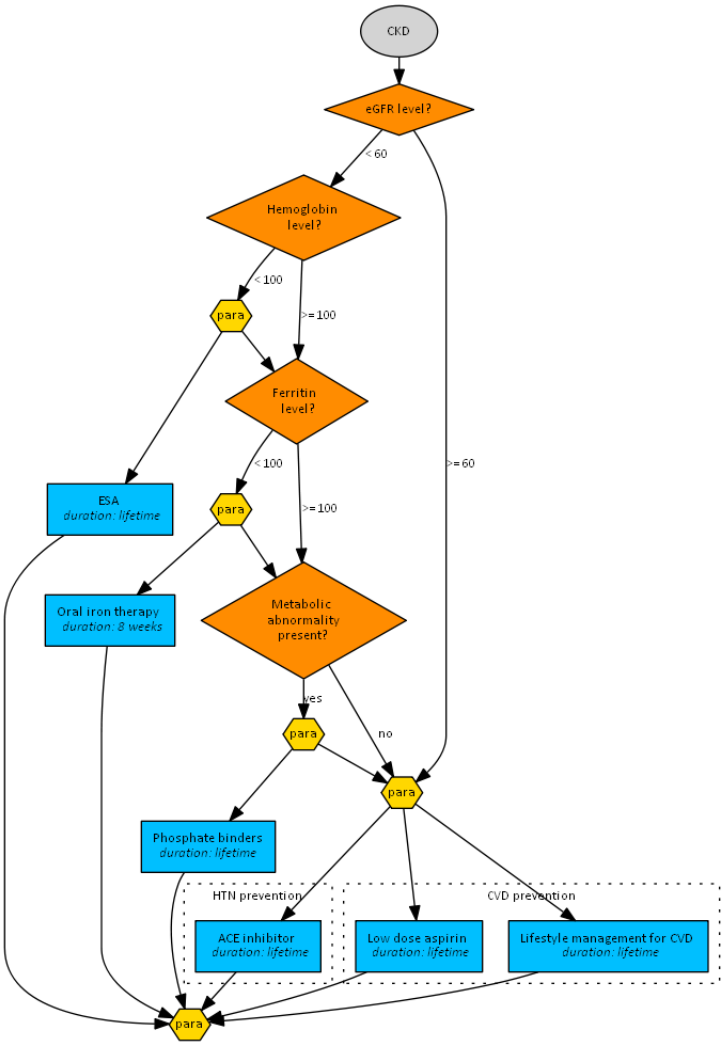

Figure 11: AG for CKD

Processing

The focus of our approach is on representation. Once the mitigation problem is represented as a planning problem, the processing and reasoning are carried out by the planner. Figure 12 shows an overview of the representation and processing steps for use case 2. The encoding of a problem instance involves four main elements that we describe in detail below: patient data and preferences (including a planning horizon), interactions and revision operators, the hybrid AG-RO model, and the objective function.

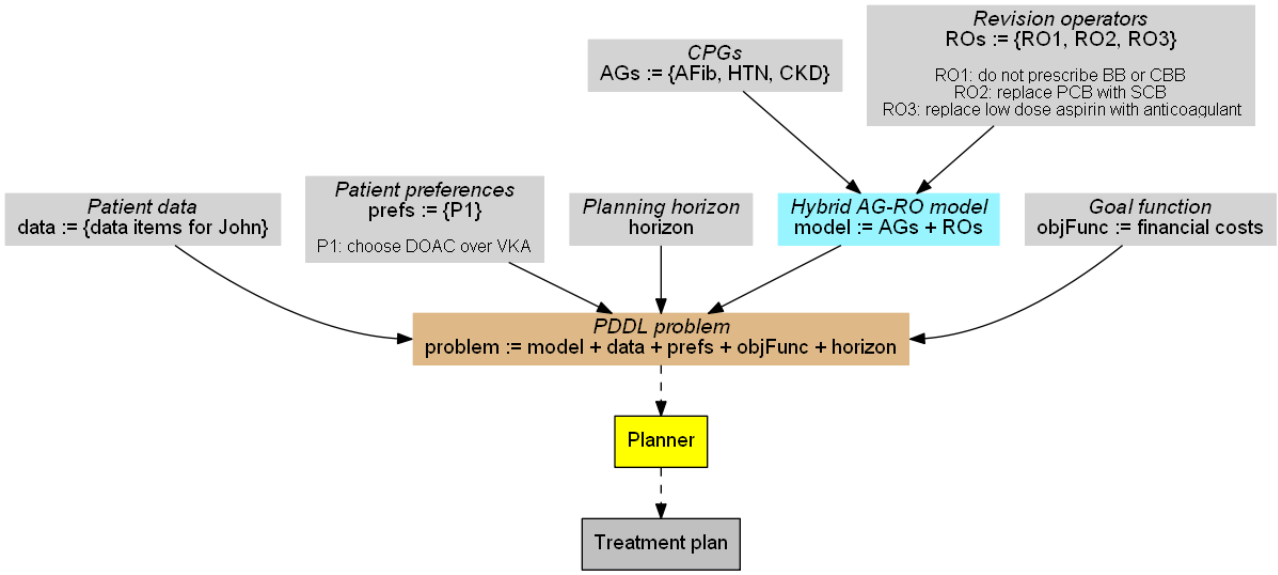

Figure 12: Overview of representation and processing for use case 2

Patient data and preferences

This use case considers the case of John, a 70 year old male diagnosed with CKD and HTN. A patient with advanced CKD may also suffer from metabolic and nutritional disturbances and as a result, be at risk of developing cardiovascular disease (CVD). Recently John has also experienced irregular heartbeat and been diagnosed with AFib. He has decreased kidney function (eGFR levels are less than 30), and has anemia (hemoglobin level of 95) requiring him to take an ESA medication. John does not have any metabolic disturbances and has a stable ferritin level of 110. Figure 15 shows how the patient data for the three diseases is represented in the PDDL code.

John prefers DOAC to warfarin for an anticoagulant. Patient preferences are captured via *execution costs* in our model. All action nodes have a cost associated with them and the default objective function is to minimize total cost. Preferences are over the alternative action nodes in the AG. We assume these alternatives are already present in the AG and patient preference information simply indicates which alternative is preferred. In this instance, the cost of DOAC is set to be lower than that of warfarin, ensuring that an optimal plan includes DOAC, if possible.

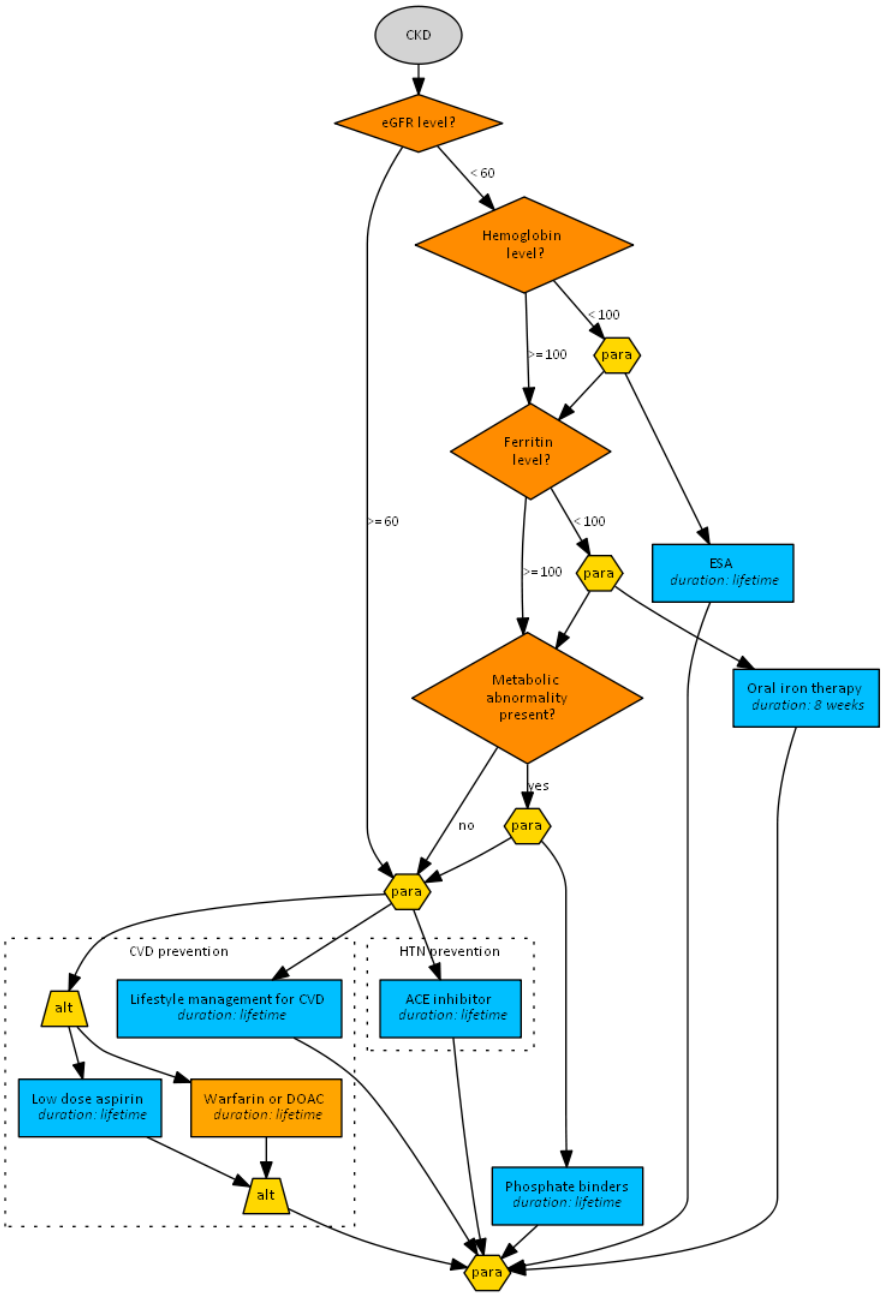

Figure 13: Expanded AG for CKD

Interactions and revision operators

- Do not prescribe BB medication: John should be prescribed BB for rate control and recurrence prevention in long term AFib therapy. However, combining BB medication with an ACE inhibitor or with CCB is not recommended, so BB medication can not be prescribed. When a patient is diagnosed with both AFib and HTN diseases, the action node for taking BB in the AG for AFib is replaced with a revision action that does nothing. Thus the relevant adverse interaction is identified (A1, A2) and mitigated (B5).

- Replace PCB with SCB: Since John has been diagnosed with AFib, his anti-arrhythmic therapy might include a potassium channel blocker (PCB) such as amiodarone. However, amiodarone is counter indicated for patients diagnosed with CKD and it is advised to prescribe a sodium channel blocker (SCB) such as propafenone. When patient has been diagnosed with AFib and CKD diseases, the action node for taking a PCB in the AG for AFib is replaced with a revision action for taking a SCB. That is, the relevant adverse interaction is identified (A1, A2) and mitigated (B4, B5).

- Replace low dose aspirin with warfarin or DOAC: John takes low dose aspirin to lower the risk of CVD. However, given that John has AFib, CVD prevention must now involve an anticoagulant such as warfarin. John's preference is for DOAC. Here we have a revision that also involves a preference in the selection of the revision action to replace the originally recommended course of action (C1).

Hybrid AG-RO model

The hybrid AG-RO model for this use case is as follows.

- The AG for AFib is expanded to include an action node for SCB as indicated by potentially applicable revision operator. Similarly, the AG for CKD is expanded to include a node for DOAC. In addition, null nodes are introduced to the AG for AFib, which may be traversed by the planner instead of the nodes for BB/CBB, if an adverse interaction requires that these medications not be prescribed.

- A triggering sequence identifying the presence of each of the three interactions is encoded. For example, the triggering sequence for "replace PCB with SCB" indicates that the node representing PCB (dronedarone or flecainide or amiodarone) is part of an interaction.

Objective function

The metrics used in the objective function are financial cost, patient's burden, and nonadherence likelihood. Financial cost refers to the cost of an action or treatment step (e.g., the annual cost of warfarin medication is $55). Patient's burden refers to the effort required to carry out a particular treatment (e.g., patients on warfarin must get a weekly blood test). Nonadherence likelihood refers to the likelihood that a patient may not adhere to the prescribed treatment (e.g., because patient on warfarin must submit to a weekly blood test, he/she is more likely then if treated with DOAC (i.e. Dabigatram) that involves only a scheduled visit with a specialist). We represent the nonadherence likelihood as a cost of nonadherence.

```
0.000: (makefirstdecision d2 egfr hemoglobin) [0.000]
0.001: (takefirstaction d3 lifestyle age55) [0.000]
0.001: (makedecisiontoactionnode d2 hemoglobin esalife) [0.000]
0.002: (takefirstaction d warfdoac spcircum) [0.000]
0.002: (makedecisiontoactionnode d3 age55 ccb12wks) [0.000]
0.003: (takeactiontodecisionnode d2 esalife ferritin) [0.000]
0.003: (makedecisiontodecisionnode d spcircum afibtype) [0.000]
0.004: (takeactiontodecisionnode d3 ccb12wks bpcontrol2) [0.000]
0.004: (makedecisiontodecisionnode d2 ferritin metabolicabnormality) [0.000]
0.004: (makedecisiontoactionnode d afibtype cardio) [0.000]
0.005: (makedecisiontoparallelblock d2 metabolicabnormality p5) [0.000]
0.005: (makedecisiontoparallelblock d3 bpcontrol2 p1) [0.000]
0.006: (takeactiontodecisionnode d cardio improve) [0.000]
0.007: (takeparallelactionnorevisions d3 p1 pdiuret12wks pdi12wks_end) [0.000]
0.007: (takeparallelactionnorevisions d3 p5 paspirinlife panticoaglife_end) [0.000]
0.007: (takeparallelactionnorevisions d3 p5 paceinhiblife paceinhiblife_end) [0.000]
0.007: (takeparallelactionnorevisions d3 p1 pace12wks pace12wks_end) [0.000]
0.007: (makedecisiontodecisionnode d improve afibrecur_tachycardia) [0.000]
0.008: (makedecisiontoparallelblock d afibrecur_tachycardia p9) [0.000]
0.008: (takeparallelaction d2 p5 plifestyle plifestyle_end) [0.000]
0.010: (takeparallelactionnorevisions d3 p5 newpdoaclife panticoaglife_end) [0.000]
0.010: (takeparallelactionnorevisions d3 p9 newnobb pbbcbbdlife_end) [0.000]
0.010: (takeparallelactionnorevisions d3 p9 bbcbbdlife pbbcbbdlife_end) [0.000]
0.011: (exitparallelblocktodecision d3 p2 bpcontrol3) [0.000]
0.011: (takeparallelaction d p9 newscb pdfa_end) [0.000]
0.012: (makedecisiontoparallelblock d3 bpcontrol3 p3) [0.000]
0.014: (takeparallelactionnorevisions d3 p3 pspecialist1hr pspec_end) [0.000]
0.014: (takeparallelactionnorevisions d3 p3 pdiuretlife pdiuretlife_end) [0.000]
0.014: (takeparallelactionnorevisions d3 p3 pccblife pccblife_end) [0.000]
0.014: (takeparallelactionnorevisions d3 p3 pacelife pacelife_end) [0.000]
0.019: (exitparallelblocktogoal d3 p4 g3) [0.000]
0.020: (exitparallelblocktogoal d2 p6 g2) [0.000]
0.021: (finalgoalreached d3 g3) [0.001]
0.021: (exitparallelblocktogoal d p10 g) [0.000]
0.024: (finalgoalreached d2 g2) [0.001]
0.025: (finalgoalreached d g) [0.001]
```

Figure 14: Internal plan for use case 2: AFib, HTN, CKD

Each node in the hybrid AG-RO model is assigned a value for each of these metrics. The objective function minimizes a weighted sum of these metrics, where the weights are chosen to reflect metrics' relative importance for a patient encounter (C1, C2). An example objective function is, $minimize\ [0.2 * cost + 0.6 * burden + 0.2 * nonadherence]$.

Because this use case does not define any priorities or planning horizons, all three goal nodes pertaining to the three diseases are treated equally and must be reached when finding a plan corresponding to optimal treatment. If we wanted to prioritize treatments for specific diseases or allow for the partial treatment of a disease (e.g., treating AFib and CKD is higher priority than treating HTN), we could use a combination of an objective function and a planning horizon to support the satisfaction of partial clinical goals when defining the planning goal (C2, C4).

Output

The OPTIC planner is run on the domain file and the use case problem file, and an optimal treatment plan is generated. The planner outputs an internal plan that can be easily post-processed to remove details of the execution, and the treatment plan is presented to the patient and physician in a more user friendly format. Figure 14 shows the internal plan generated by the OPTIC planner.

```
;;AFib
;;V1 = 7
(= (patientValue d SPCIRCUM BBCBBD4WKS) 7)
(= (patientValue d SPCIRCUM AFIBTYPE) 7)

;;V2 = 7
(= (patientValue d AFIBTYPE HIGHRECUR) 7)
(= (patientValue d AFIBTYPE CARDIO) 7)

;;V3 = 7
(= (patientValue d RESOLVE AFIBTYPE) 7)
(= (patientValue d RESOLVE BBCBBDLIFE) 7)
(= (patientValue d RESOLVE newNoBB) 7)

;;V4 = 7
(= (patientValue d HIGHRECUR PILL) 7)
(= (patientValue d HIGHRECUR DFA) 7)
(= (patientValue d HIGHRECUR newSCB) 7)

;;V5 = 7
(= (patientValue d IMPROVE BBCBBDLIFE) 7)
(= (patientValue d IMPROVE AFIBRECUR_TACHYCARDIA) 7)
(= (patientValue d IMPROVE newNoBB) 7)

;;V6 = 9
(= (patientValue d AFIBRECUR_TACHYCARDIA G) 9)
(= (patientValue d AFIBRECUR_TACHYCARDIA DFA) 9)
(= (patientValue d AFIBRECUR_TACHYCARDIA BBCBBDLIFE) 9)
(= (patientValue d AFIBRECUR_TACHYCARDIA P9) 9)
(= (patientValue d AFIBRECUR_TACHYCARDIA newSCB) 9)
(= (patientValue d AFIBRECUR_TACHYCARDIA newNoBB) 9)


;;CKD
;;V1 = 25
(= (patientValue d2 eGFR HEMOGLOBIN) 25)
(= (patientValue d2 eGFR P5) 25)

;;V2 = 95
(= (patientValue d2 HEMOGLOBIN ESALIFE) 95)
(= (patientValue d2 HEMOGLOBIN FERRITIN) 95)

;;V3 = 110
(= (patientValue d2 FERRITIN ORALIRON8WKS) 110)
(= (patientValue d2 FERRITIN METABOLICABNORMALITY) 110)

;;V4 = 0 (No)
(= (patientValue d2 METABOLICABNORMALITY P5) 0)
(= (patientValue d2 METABOLICABNORMALITY P7) 0)


;;HTN
;;V1 = 0 (No)
(= (patientValue d3 AGE55 CCB12WKS) 0)
(= (patientValue d3 AGE55 ACE12WKS) 0)

;;V2 = 0 (No)
(= (patientValue d3 BPCONTROL2 P1) 0)
(= (patientValue d3 BPCONTROL2 G3) 0)

;;V3 = 0 (No)
(= (patientValue d3 BPCONTROL3 P3) 0)
(= (patientValue d3 BPCONTROL3 G3) 0)
```

Figure 15: Patient data for use case 2: AFib, HTN, CKD

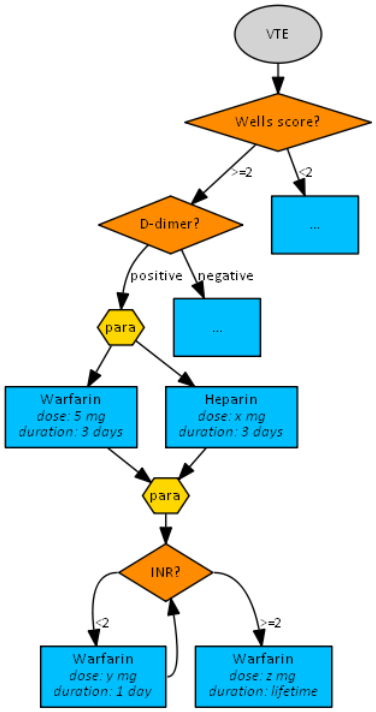

Figure 16: Actionable Graph for VTE

Part 3: Implementation of the Case Studies: Use Case 3

Input

The input to MitPlan 2.0 consists of the AGs derived from the CPGs corresponding to the two diseases in the use case, patient data and preferences, and revision operators. This use case does not specify a planning horizon. No metrics are specified and the use case does not involve an objective function. Therefore, we use the default objective function with execution costs as described in Part 1. Figures 16 and 17 depict the AGs for venus thromboembelism (VTE) and urinary tract infection (UTI) respectively. In these figures we focus on those parts of CPGs that are relevant for the use case, therefore some paths (e.g., for Wells score < 2) are omitted for brevity. The patient scenario and input data are explained in the next section.

Processing

The encoding of a problem instance, processed by the planner, involves four main elements described next: patient data and preferences (including a planning horizon), interactions and revision operators, the hybrid AG-RO model, and the objective function.

Patient data and preferences

This use case describes the situation of a 67 year old female with an existing condition, recurrent VTE, who is subsequently also diagnosed with UTI. We do not consider any patient preferences in this use case.

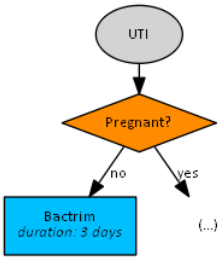

Figure 17: Actionable Graph for UTI

Interactions and revision operators

In order to generate a treatment plan for this case, MitPlan 2.0 adds a revision operator that reduces the dosage of medication. The revision operator takes as input the amount of reduction required (e.g., reduce dosage by 10%) thereby providing flexibility on the amount of reduction. The guideline also requires that the dosage should be re-evaluated after the third day of therapy based on the risk of bleeding, as measured by the international normalized ratio (INR) value. This is modelled using durative actions, such that the actions prescribing warfarin (4.5 mg / day) and bactrim (2 regular strength tablets / day) have a time duration of 3 days and the re-evaluation actions begin on day 3 of the treatment. During re-evaluation, the INR is measured daily and warfarin adjusted accordingly with the goal of achieving an INR value that is greater than or equal to 2. The planner uses durative actions to simulate the time durations in the guideline. This use case involves features A2, B2, B3, C1.

Hybrid AG-RO model

The hybrid AG-RO model for this use case is as follows.

- The AG for VTE is expanded to include an action node that reduces the dosage of warfarin, taking as input the amount of reduction required.
- Since patient data confirms a diagnosis of UTI, the RO is triggered. A triggering sequence indicates that there is an adverse interaction between warfarin and bactrim.

Objective function

The planner minimizes total execution cost since no metrics are specified for this use case. Execution costs are explained in Part 1.

Output

The planner is run on the domain file and the use case problem file, and an optimal treatment plan is generated. The planner outputs an internal plan that can be easily post-processed to remove details of the execution of the planner and the final treatment plan is presented to the patient and physician. Figure 18 shows the internal plan for this use case.

```
0.000: (makefirstdecision d1 wells_score d_dimer)  [0.000]
0.001: (makedecisiontoparallelblock d1 d_dimer p1)  [0.000]
0.003: (takeparallelaction d1 p1 heparin heparin_end)  [72.000]
0.003: (takeparallelaction d1 p1 reducedosewarfarin reducedosewarfarin_end)  [72.00
0.003: (takeactiontogoal d2 bactrim g2)  [72.000]
72.005: (finalgoalreached d2 g2)  [0.001]
72.005: (exitparallelblocktodecision d1 p2 inr)  [0.000]
72.006: (makedecisiontoactionnode d1 inr warfarin)  [0.000]
72.007: (takeactiontogoal d1 warfarin g1)  [24.000]
96.009: (finalgoalreached d1 g1)  [0.001]
```

Figure 18: Internal plan for use case 3: VTE, UTI

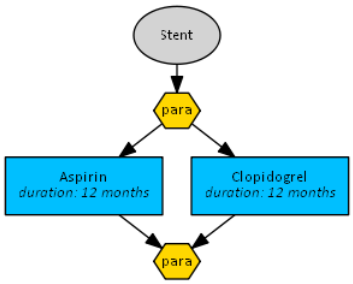

Figure 19: AG for post-stent surgery

Part 3: Implementation of the Case Studies: Use Case 4

Input

The input to MitPlan 2.0 consists of the AGs derived from the CPGs corresponding to the two diseases in the use case, patient data, planning horizon, and revision operators. This use case does not specify any patient preferences. No metrics are specified and the use case does not involve an objective function. Therefore, we use the default objective function with execution costs as described in Part 1. Figures 19, and 20 depict the AG for drug-eluting stent and lung mass surgery respectively. The patient scenario and data are presented in detail in the next section.

Processing

The encoding of a problem instance, processed by the planner, involves four main elements described next: patient data and preferences (including a planning horizon), interactions and revision operators, the hybrid AG-RO model, and the objective function.

Patient data and preferences

In this use case, we consider a 73 year old male patient who has undergone surgery to implant a drug-eluting stent, and who, 2 months later, is diagnosed with a lung mass requiring further surgery which cannot be postponed. The patient is considered at high risk of surgical bleeding. The current treatment plan post stent surgery is to take aspirin (81 mg daily) and clopidogrel (75 mg daily) for 12 months. In the days leading up to the lung mass surgery this treatment plan must be revised in preparation for the surgery.

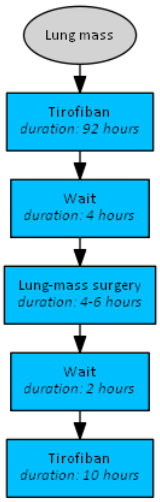

Figure 20: AG for lung mass surgery

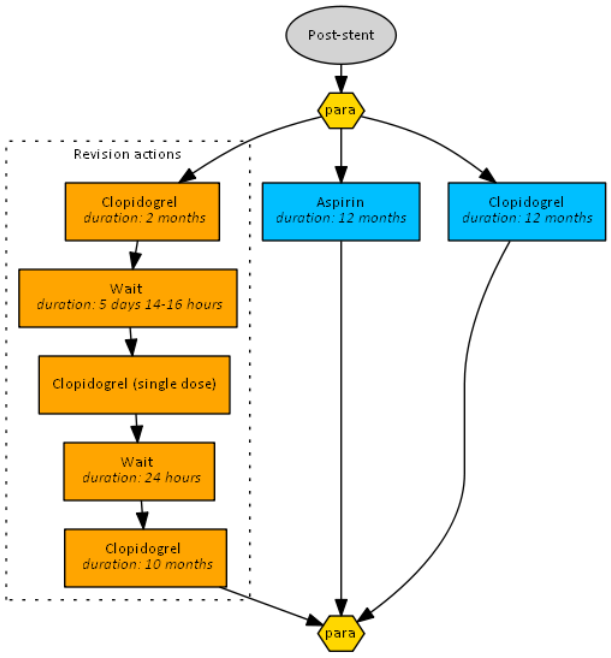

Figure 21: Expanded AG for post-stent surgery

Interactions and revision operators

The following set of revision actions are carried out. Five days or 120 hours before surgery, clopidogrel is stopped (aspirin continues to be administered). Four days or 96 hours before surgery, tirofiban is given intravenously for a duration of 92 hours. Thus tirofiban is stopped 4 hours prior to surgery. The surgery is commenced and lasts 4-6 hours. Two hours after surgery tirofiban is restarted and administered for a period of 10 hours. Immediately thereafter, a single dose of clopidogrel (300 mg) is given. Twenty-four hours after the single dose, clopidogrel is resumed at the dosage of 75 mg daily. Aspirin and clopidogrel are stopped once 12 months have passed since the stent surgery. MitPlan 2.0 processes this case using durative actions as well as revision operators. This use case involves the following features: A3, A6, B5, B6, C1.

Hybrid AG-RO model

The hybrid AG-RO model for this use case is described below. The planner seeks to find an optimal path to the goal that incorporates the set of actions required to prepare for the second surgery.

- The AG for drug-eluting stent is expanded to include the set of revision actions described above (see Figure 21).
- Since patient data indicates that this patient must undergo surgery due to a lung mass diagnosis, and that this lung mass surgery cannot wait until the therapy for drug-eluting stent is completed, the revisions are triggered.

Objective function

The planner minimizes total execution cost since no metrics are specified for this use case. Execution costs are explained in Part 1.

Output

The planner is run on the domain file and the use case problem file in order to generate an optimal treatment plan. The internal plan produced can be easily post-processed to remove execution details, and the final treatment plan is presented to the patient and physician. Figure 22 shows the internal plan for this use case.

```
0.000: (executeparallelstartnode d1 p1) [0.000]
0.001: (takeparallelaction d1 p1 aspirin aspirin_end) [8760.000]
0.001: (takeparallelaction d1 p1 clopidogrel wait24hrs) [1460.000]
8760.002: (takeparallelaction d1 p1 wait24hrs wait112hrs) [24.000]
8784.003: (takeactiontoactionnode d2 tirofiban wait4hrs) [92.000]
8876.004: (takeactiontoactionnode d2 wait4hrs lungsurgery) [4.000]
8880.005: (takeactiontoactionnode d2 lungsurgery wait24hrs) [6.000]
8886.006: (takeactiontoactionnode d2 wait2hrs tirofiban) [2.000]
8888.007: (takeactiontogoal d2 tirofiban g2) [10.000]
8898.008: (takeparallelaction d1 p1 clopidogrel_singledose wait24hrs) [0.000]
8898.009: (takeparallelaction d1 p1 wait24hrs clopidogrel) [24.000]
8898.009: (finalgoalreached d2 g2) [0.001]
8922.010: (takeparallelaction d1 p1 clopidogrel clopidogrel_end) [7138.000]
16060.012: (exitparallelblocktogoal d1 p2 g1) [0.000]
16060.013: (finalgoalreached d1 g1) [0.001]
```

Figure 22: Internal plan for use case 4: Drug-eluting stent, Lung mass surgery

References

1. *MitPlan 2.0: Enhanced Support for Multi-Morbid Patient Management Using Planning*, Martin Michalowski, Malvika Rao, Szymon Wilk, Wojtek Michalowski, and Marc Carrier, Proceedings of the 19th International Conference on Artificial Intelligence in Medicine (AIME 2021), pp. 276–286, 2021.

2. *A Planning Approach to Mitigating Concurrently Applied Clinical Practice Guidelines*, Martin Michalowski, Szymon Wilk, Wojtek Michalowski, and Marc Carrier, Artificial Intelligence in Medicine, Volume 112, February 2021, 102002.