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Abstract

In this work, a constrained multi-objective function formulation of liver machine perfusion (MP) based on widely accepted viability criteria and network metabolic efficiency is described. A novel Monte Carlo method is used to improve machine perfusion (MP) performance by finding optimal temperature policies for hypothermic machine perfusion (HMP), mid-thermic machine perfusion (MMP), and subnormothermic machine perfusion (SNMP). It is shown that the multi-objective function formulation can exhibit multiple maxima, that greedy optimization can get stuck at a local optimum, and that Monte Carlo optimization finds the best temperature policy in each case.

Keywords (separated by '-'): Multi-objective optimization - Monte Carlo - Machine perfusion

Monte Carlo Optimization of Liver Machine Perfusion Temperature Policies

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Abstract. In this work, a constrained multi-objective function formulation of liver machine perfusion (MP) based on widely accepted viability criteria and network metabolic efficiency is described. A novel Monte Carlo method is used to AQ1 improve machine perfusion (MP) performance by finding optimal temperature policies for hypothermic machine perfusion (HMP), mid-thermic machine perfusion (MMP), and subnormothermic machine perfusion (SNMP). It is shown that the multi-objective function formulation can exhibit multiple maxima, that greedy optimization can get stuck at a local optimum, and that Monte Carlo optimization AQ2 finds the best temperature policy in each case.

Keywords: Multi-objective optimization · Monte Carlo · Machine perfusion

1 Introduction

Machine perfusion (MP), in which an organ is placed in chamber at *fixed* temperature and constantly supplied with nutrients (called a perfusate) containing dissolved oxygen through recirculation of the perfusate, is rapidly gaining acceptance as a better alternative to static cold storage (SCS) for the preservation of organs (i.e., kidney, liver, heart) for transplantation. Machine perfusion protocols are often classified based on the temperature of the perfusion chamber [1]. The most common protocols are Hypothermic (HMP, 0–12 °C), Mid-thermic (MMP, 13–20 °C), Subnormothermic (SNMP, 21–34 °C), and Normothermic (NMP, 35–37 °C) MP. There are also various metrics used for establishing organ viability for transplantation. However, those based on the energy state of the organ (i.e., ATP content or energy charge) seem to be the most widely accepted metrics for predicting transplantation success [2, 3]. In this paper, the terms protocol, profile, and policy, have the same meaning.

While conventional temperature protocols for MP use a fixed temperature, recent clinical studies [4, 5] in kidney MP have shown that gradual rewarming to body temperature (37 °C) improves the energy state of kidneys compared to conventional HMP and MMP. Recent optimization results using greedy and Monte Carlo optimization [7] and a metabolic model of the liver [6] also yield *discrete* policies that systematically raise the temperature of the perfusion chamber to body temperature and show improvements

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in the energy state of liver cells compared to conventional SNMP and NMP. See Fig. 1. We note that the temperature policy for Monte Carlo optimization shown in Fig. 1 has the same shape as the results for gradual rewarming for kidney shown in Fig. 3A in [5].

The constrained optimization problem studied in [7] was based only on the liver viability criteria in [8] and formulated as follows:

$$\max_{T(t)} R: pH > 7.3;\ [lactate] < 2.3\text{mM};\ T_1 \leq T_2 \leq \cdots \leq T_N \tag{1}$$

where $T(t) = \{T_1, T_2, \ldots, T_N\}$ is a discrete temperature policy, N is the number of discrete temperature adjustments, and the reward, R, is defined by

$$R = w_1|Glc| + w_2ATP + w_3Mev + w_4EC \tag{2}$$

Glc in Eq. 2 denotes glucose consumption, ATP is net ATP synthesis, Mev denotes mevalonate production, which was used as a measure of bile synthesis, EC is energy charge, and w_1 through w_4 are weights.

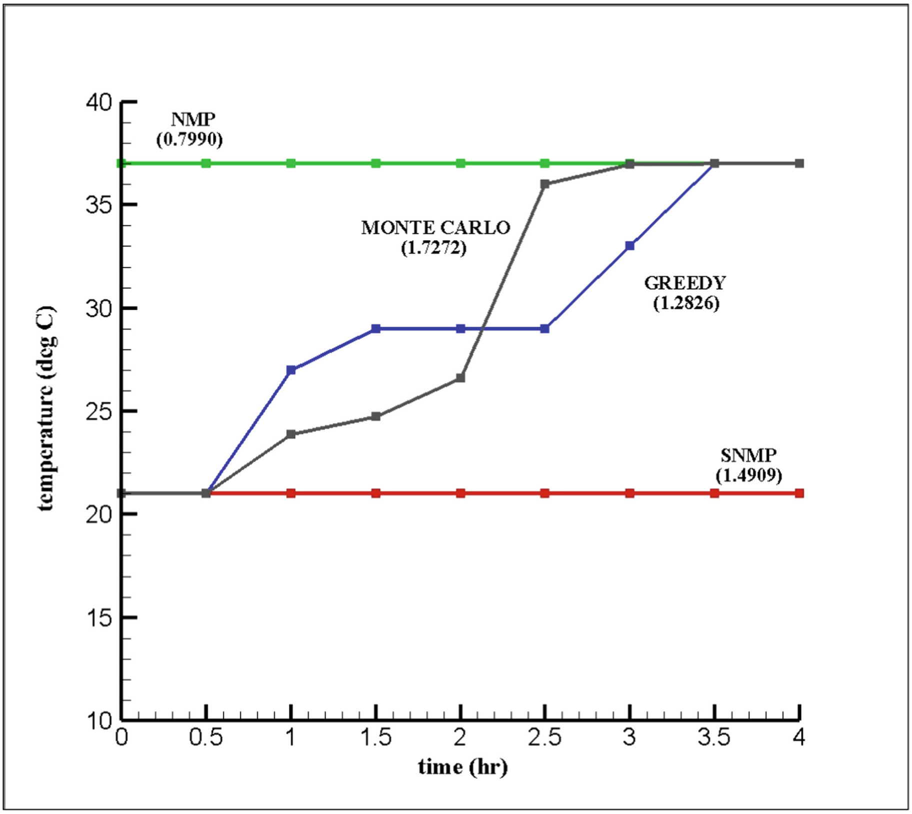

Fig. 1. Liver machine perfusion temperature policies for SNMP, NMP, GREEDY, and MONTE CARLO. Numbers in parenthesis represent amounts of ATP generated in pmol/cell.

1.1 SNMP Monte Carlo Temperature Policy Optimization and Statistics

The SNMP temperature policy optimizations in [7] were initialized to a flat temperature protocol of 21 °C. Random temperature changes for each Monte Carlo cycle (or episode) were permitted every 30 min over the course of 4 h and 3000 Monte Carlo cycles (or episodes) were used for each optimization run, which proved sufficient to find the optimal temperature policy shown in Fig. 1.

One of the more interesting aspects of Monte Carlo temperature optimization from an SNMP starting profile from the study conducted in [7] was the observation that there were three distinct levels of reward (i.e., two maxima in the reward function) – two local maxima at ~2.87 and 3.08 and a global maximum at ~3.55. Moreover, the existence of multiple optimal solutions did not appear to be an artifact of the modeling since both greedy and Monte Carlo optimization gradually warmed the perfusion chamber to body temperature and improved SNMP performance. In addition, we observed that Monte Carlo optimization bounced between the two local and global maxima quite regularly, indicating that the barriers between the three optima are small. However, as the number of cycles (i.e., episodes) was increased, the *probability* associated with states (i.e., the temperature policies) became much higher for the global maximum than that of either local maximum, as shown in Table 1, where probabilities were computed by counting the number of production cycles for the local and global maxima and dividing each by the total number of production cycles. Table 1 also shows that for 3000 Monte Carlo cycles, the probability of encountering states associated with the global maximum were at least two times higher than those for the local maxima. This last fact suggests that machine learning approaches might prove useful in this application in training and deployment.

Table 1. Reward and probability of states for SNMP Monte Carlo optimization

	Reward	Probability
Optimum		
Local maximum 1	2.8716	0.0862
Local maximum 2	3.0816	0.3029
Global maximum	3.5548	0.6078

1.2 Optimal Temperature Policies for HMP, MMP and SNMP Initial Profiles

To get a more complete understanding of the performance of Monte Carlo optimization, optimal temperature policies were also determined for HMP and MMP. As in the case for SNMP, initial profiles for HMP and MMP were taken as flat temperature profiles of 6 and 16 °C, respectively, Monte Carlo optimization temperature changes were permitted every 30 min, machine perfusion was run for 4 h, and 3000 episodes were used to find the optimal temperature policy.

Figure 2 shows a comparison of all three cases where it is interesting to note the following: (1) the optimal temperature policy is different in each case, (2) the colder the initial temperature profile is, the more rapid is the rise during the first 2.5 h of operation, (3) all global optimal solutions have an energy charge at the low end of the normal range [0.6, 0.95], and (4) it is somewhat surprising that mid-thermic machine perfusion synthesizes the largest amount of net ATP.

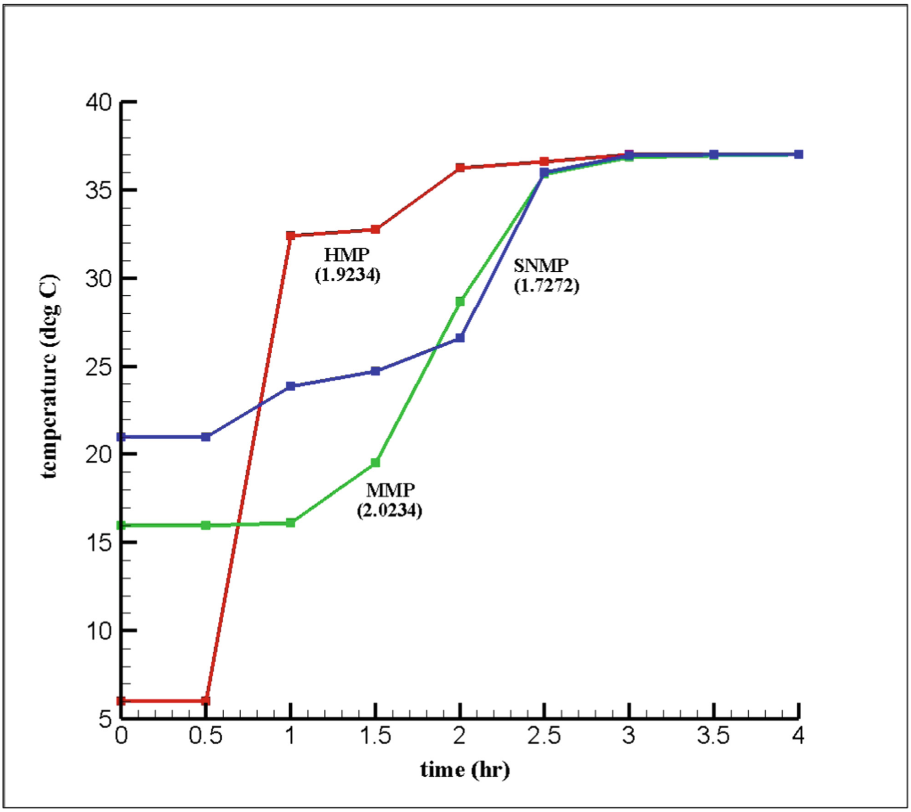

Fig. 2. Liver machine perfusion globally optimal temperature policies from initial profiles for HMP, MMP, and SNMP. Numbers in parenthesis represent amounts of ATP generated in pmol/cell.

2 Multi-objective Optimization of MP Temperature Profiles

The constrained optimization problem described in Eqs. 1 and 2 does not consider network metabolic efficiency, E. Here we include network metabolic efficiency by adding the following objective to the problem formulation

$$\max E = \frac{net\,ATP}{|Glc|} \tag{3}$$

Equations 1, 2 and 3 strike a balance between pure reward and network metabolic efficiency and give rise to a Pareto optimal front. To illustrate this, we chose to apply multi-objective optimization to MMP since it provided the 'best' optimal solution in Fig. 2 as measured by net ATP produced.

2.1 Multi-objective Optimization of MMP

For MMP, each of the eight temperatures in the initial temperature policy was set to 16 °C and each episode for MMP was the same as that for earlier studies of SNMP. That is, the liver was flushed with University of Wisconsin (UW) solution and then placed in static cold storage (SCS) at 4 °C for 6 h. SCS was then followed by 4 h of machine perfusion. See [6, 7] for details.

Using 3000 Monte Carlo episodes, multi-objective optimization with an initial MMP temperature profile produced the discrete objective function sets and Pareto optimal front shown in Fig. 3.

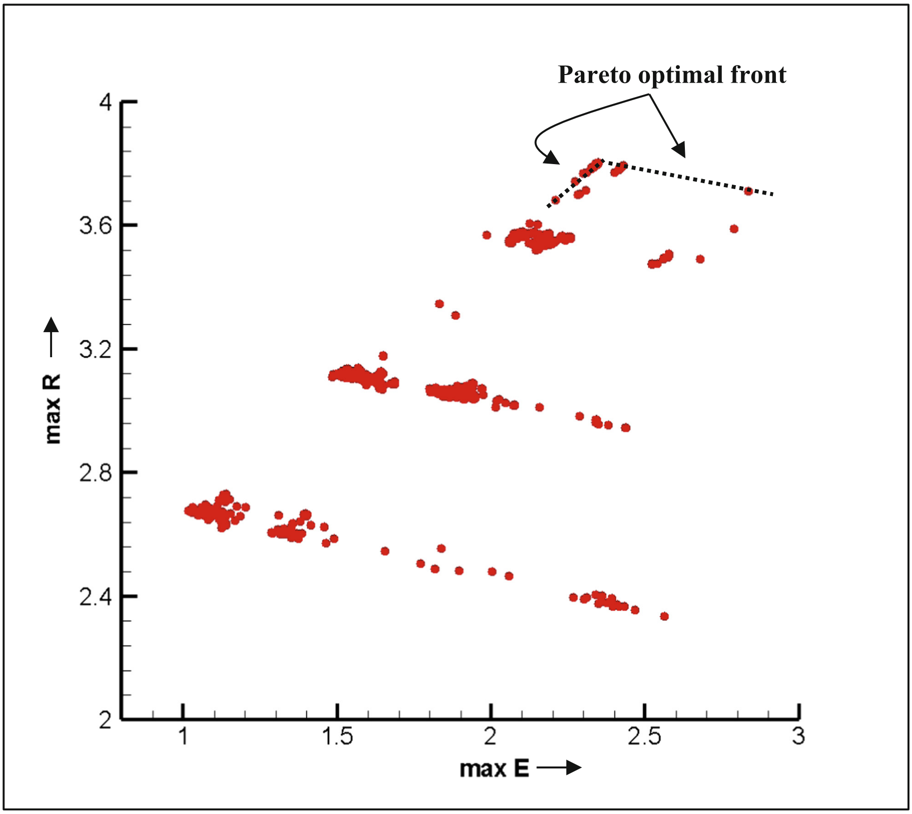

Fig. 3. Pareto set and optimal front for mid-thermic machine perfusion

Note that the Pareto optimal set (dotted lines) is rather flat in R and shows more variation with respect to network metabolic efficiency, E. In addition, there is virtually no discernable difference in the best temperature policies along the Pareto optimal front. On the other hand, the most significant differences lie in the metabolic behavior of glycolysis and malonyl-CoA synthesis, the latter of which is a driver of fatty acid synthesis and α-oxidation. Comparable results were obtained for the Pareto sets and optimal fronts computed from initial flat HMP and SNMP temperature profiles.

3 Discussion of Results

In this section, the machine perfusion optimization results are discussed along with the performance of the Monte Carlo algorithm.

3.1 Machine Perfusion Optimization

The results shown in Figs. 1, 2 and 3 show that Monte Carlo temperature policy optimization is an effective tool for improving the performance of liver machine perfusion. Using a constrained multi-objective function derived from (1) a reward function based on clinical liver viability criteria [8] and (2) network metabolic efficiency measured in terms of net ATP synthesized per amount of glucose consumed, temperature policy optimization improved net ATP synthesis, energy charge, and bile production while clearing lactate and maintaining pH within the physiological range for healthy liver cells from the following static cold storage results: lactate concentration was 4.11 mM, the energy charge of the cell was 0.4395, and the pH was 8.93. In addition, the results in Figs. 1 and 2 are consistent with recent clinical results in gradual warming [4, 5].

3.2 Algorithm Performance

The constrained optimization formulation given by Eqs. 1–3 is novel in that it is a multi-objective function that accounts for gradual warming, constraints on the temperature policy, viability constraints, and network metabolic efficiency.

In this work, Monte Carlo acceptance ratios ranged from 0.1 to 0.37, which is within the usual range of ‘good’ acceptance ratios for Monte Carlo methods. In all cases, the algorithm found the global maximum in under 3000 Monte Carlo cycles. Computer times required for the temperature policy optimizations with 3000 Monte Carlo cycles averaged 1335 CPU sec (0.37 CPU hrs.). However, it is important to note that episodes tend to jump back and forth between the global and local maxima suggesting that the barriers between all maxima (i.e., valleys) were shallow and presented little resistance to movement on the reward surface.

Another point of interest is the fact that the global maximum in reward found from an initial SNMP temperature profile was *different from* the global maximum in reward found from either the initial HMP or MMP temperature profile and this was a bit confusing at first. Two additional considerations are important here. First, when the number of Monte Carlo cycles for the optimization starting with an SNMP temperature profile was increased to 5000, the algorithm still did not find a global maximum with a reward value of ~3.8. Second, using a different initial temperature profile of 28 °C, which is midway in the region classified as SNMP, the resulting global maximum reward changed only slightly from 3.5548 to 3.5619. Thus, it appears that using initial SNMP temperature profiles may preclude the existence of the global maximum that occurs when initial HMP and MMP temperature profiles are used.

4 Conclusions

A multi-objective function consisting of (1) a reward function based on liver viability criteria [8] and (2) a measure of network metabolic efficiency along with Monte Carlo optimization were used to determine globally optimal temperature policies for a mathematical model of liver metabolism during machine perfusion. Initial temperature policies corresponded to traditional hypothermic, mid-thermic, and subnormothermic temperature profiles. In each case, the global optimum temperature policy was determined within a reasonable number of Monte Carlo cycles (episodes). See Fig. 2. However, optimization results varied depending on the initial temperature profile.

No single initial temperature profile gave the best results for all terms in the reward function. The best overall results were obtained when the Monte Carlo optimizations were initiated from a MMP temperature profile. In addition, the probability of finding the global maximum reward of ~3.8 was much higher in this case than when the optimizations were started from an initial HMP temperature profile. It also came as a surprise that starting from an initial SNMP temperature profile yielded results that were not as good as those for MMP.

A Pareto set and optimal front were determined for mid-thermic machine perfusion. Results here showed that the objective function set is discrete, that the Pareto optimal front is flat in terms of the reward function and that all solutions along the front result in essentially the same optimal temperature policy. On the other hand, the network metabolic efficiency varied considerably along the Pareto optimal front, suggesting that other factors in addition to those in the multi-objective formulation may play a role in determining liver metabolism during machine perfusion.

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Chapter 22

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